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THE FLUIDS OF THE BODY

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THE MERCERS' COMPANY LECTURES

ON

THE FLUIDS OF THE BODY

BY

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PREFACE

The first seven of the Lectures contained in this volume are based on two courses of Lectures which I delivered at University College, London, in the summer of 1907, and in New York during January, 1908, at the Bellevue Hospital and Medical School, under the foundation of Dr. C. A. Herter. The eighth Lecture represents one of the Arris and Gale Lectures delivered in 1896 before the Royal College of Surgeons with certain additions and alterations necessitated by recent work on the subject. I have thought it advisable to add this last chapter in order that those, whose interests lie chiefly in the practical treatment of disease, may appreciate how closely our control of morbid processes is bound up with the advance of the purely physiological knowledge which forms the theme of the first seven Lectures.

I have made no attempt to give an exhaustive account of any of the subjects treated in the Lectures, believing that a presentation from the standpoint of one worker is more likely to excite interest, whether of sympathy or dissent. In this way my readers may be stimulated to search out for themselves, in the wards or in the laboratory, the answers to some of the riddles with which they are here confronted.

ERNEST H. STARLING.

40, West End Lane, N.W.,
January, 1909.

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THE FLUIDS OF THE BODY

LECTURE I

PHYSICAL PROPERTIES OF PROTOPLASM

In all living organisms, whether belonging to the animal or vegetable kingdom, the presence of water as an integral part of their structure seems to be essential for the manifestation of any vital phenomenon.

It is a familiar fact that the activity of even the lowest forms of life cannot be displayed in the absence of this substance. Highly unstable materials, such as dead tissues of animals themselves, if thoroughly dried can be kept indefinitely without the slightest sign of putrefaction. Access of water to such material at once creates the conditions suitable for the growth of the micro-organisms which bring about putrefaction. Vegetable seeds undergo no change until moistened; when, almost immediately, commences the wonderful series of chemical changes which culminate in the germination of the seed and the production of a new individual.

When we call to mind the fact that, at the time that life was coming into being on the earth's surface, water was everywhere present, it is not surprising that it should have played a part in the formation of the complex self-polymerising material which formed the primitive protoplasm. If we take the unique properties of water into consideration—its fluid character, its high specific heat, its solvent powers (which are

unequalled by that of any other liquid), its ionising power over salts, we see that, having once entered into the composition of protoplasm, it must determine many of the qualities of this material and play an important part in all the chemical and physical changes which make up what we call life. Protoplasm must be regarded as a fluid and as consisting of a solution or suspension in water of compounds of very varying complexity. It follows that all the energies which are displayed by the living cell must be derived from the energies of substances in solution, and must therefore be derivable from and measurable in terms of osmotic energy, when taking place in the interior of the cell; of surface energy, when occurring at the dividing surface between the living cell and its environment.

To these two modes of energy we must ultimately be able to refer all the manifestations of life. No substance can obtain entrance into a living organism, except it be soluble. Until solution occurs, particles of food, mechanically introduced into the cell protoplasm, take no part in the cycle of processes which make up the life of the cell. All the chemical changes, which we have to study under the heading of metabolism, relate to changes in and between substances in solution. It is a common practice to speak of the energy of the body as derived from the combustion of the foodstuffs. The statement is a little dangerous if it brings too strongly to our minds the image of burning coal or other combustible material, and makes us forget that the processes of oxidation, which are responsible for the production of energy in the body and give rise to the same end-products as would the combustion of foodstuffs outside the body, *i.e.* CO_2 and H_2O, really occur by continual gradations, the oxygen and the oxydate in every case being dissolved in a watery menstruum.

The available energy of a living cell at any given moment may be regarded as made up of two factors, viz.:

A. The total osmotic pressure of all the dissolved substances present in the cell.

B. The chemical energy of these substances; *i.e.*, the total energy, which will be produced when they undergo complete oxidation.

One might speak of these two factors as the kinetic or actual, and the potential (osmotic) energy of the cell.

Since the actual energy of the cell is represented by the osmotic pressure of its dissolved molecules, and therefore depends on the total number of the molecules present, the molecular concentration of the dissolved substances in the fluid pervading the cell becomes a matter of great importance. Everyone is familiar with the fact that, for the preservation of isolated cells, it is essential to keep them in some fluid, which we designate as normal. This term being interpreted signifies merely that our normal fluid must have a certain molecular concentration. If it be hypertonic or hypotonic, we know that the cell shrivels, or swells up and bursts, as the case may be. Whereas the actual energy of any cell is determined solely by its molecular concentration at the moment, its potential energy depends on the *nature* even more than on the amount of the substances which are present in solution. According to the nature of these substances, so the reactions and the behaviour of the cell will differ. Diversity of function implies diversity of structure and composition.

Although every active cell is constantly taking up and giving out dissolved substances to the surrounding medium, and although in almost every case its external surface is freely permeable to water, in no case do the inorganic salts of a living cell bear any relation to those of its environment. Thus, even if we take such inert structures as the

red blood-corpuscles, we find a striking difference between their contained salts and those of the surrounding blood-serum. These differences are well shown in the following Table.

Inorganic Constituents of Corpuscles and Serum of Pig in 1,000 Parts (Bunge).

Inorganic Substances.	Corpuscles.	Serum.
Total	8·9	7·7
K_2O	5·543	0·273
Na_2O	0	4·272
CaO	0	0·136
MgO	0·158	0·038
Cl	1·504	3·611
P_2O_5	2·067	0·188

The same individual divergencies are found if we analyse a number of seaweeds from the same locality, all therefore bathed by the same sea-water. The following Table (page 5) shows the percentage composition of the ash of four different kinds of fucus growing in close proximity to one another at the mouth of the Clyde.*

We see that a living cell, though in constant osmotic interchange both of water and dissolved substances with its surroundings, nevertheless possesses a composition widely differing from that of the latter and determined chiefly by the nature and function, *i.e.*, by the hereditary disposition of the cell itself. Is it possible to find in the physical structure or

* E. Overton, "Ueber den Mechanismus der Resorption und der Sekretion." Nagel's "Handbuch d. Physiol. d. Menschen." Bd. II. 2te Hefte. 1906-7.

chemical composition of the material out of which the cell is built up any clue to the explanation of its behaviour?

An isolated living cell, when viewed under the microscope, appears as a translucent mass, in which, in some cases, very little trace of structural differentiation is to be seen. In other cells we make out such structures as a nucleus, contractile

—	Fucus digitatus.	F. vesiculosus.	F. nodosus.	F. serratus.
K	22·40	15·23	10·07	4·51
Na	8·29	11·16	15·80	21·15
Ca	11·86	9·78	12·80	16·36
Mg	7·44	7·16	10·93	12·66
Fe_2O_3	0·62	0·33	0·29	0·34
NaCl	28·39	25·10	20·16	18·76
NaI	3·62	0·37	0·54	1·33
SO_3	13·26	28·16	26·69	21·06
P_2O_5	2·56	1·36	1·52	4·40
SiO_2	1·56	1·35	1·20	0·43
Total ash (per cent. of dried plant)	20·04	16·39	16·19	15·63

vacuoles, permanent cavities or openings, such as the mouth, and structures attached to the surface, such as cilia. In every case the jelly-like mass has a well-defined border or line of demarcation between it and the circumambient medium.

On treating the cell in various ways, as, *e.g.*, by the use of fixing reagents and dye-stuffs, we learn the existence of differentiation, physical as well as chemical, within the minute limits of the cell. Apart from the cell organs, such as nucleus or vacuole, we find in most cases that the cytoplasm, which forms

the main substance of the cell itself, reveals signs of differentiation and betrays a reticular, or honeycomb, structure. How far such a structure is an artefact and depends on the action of reagents on a homogeneous material is still a matter of discussion. When a cell, such as the ovum, accumulates food supplies, its natural tendency is to deposit these materials in alveoli within the protoplasm, so that the whole structure acquires an alveolar arrangement which is visible in the fresh living protoplasm. Although the margin of a cell is structurally defined, and although in many cases a cell presents a form and shape which is characteristic, it is impossible to regard the protoplasm of which it is composed as a solid. The existence of active streaming movements, which may occur in opposite directions within the limits of a thin strand of protoplasm, *e.g.*, in Chara, shows that the substance, out of which the cell is built, is fluid—fluid of varying degrees of viscosity in different cells, or in different parts of one and the same cell.

The fact that a cell may have a distinct shape and a resistance to deformation may be due to the surface tension existing between the cell and its surroundings, or between different parts of the cell. A globule of mercury, though perfectly fluid, presents resistance to deformation and recovers its shape with a certain degree of energy after any deforming force has been applied. By multiplying surfaces within a fluid it is possible to rob the whole mass of most of the properties which we regard as characteristic of fluid. Thus by the addition of a little albumen to petroleum and agitation so as to break up the petroleum into droplets, each surrounded by a layer of the albuminous fluid, it is possible to turn this liquid into a material which can be handled with a shovel. Our histological experience would therefore point to protoplasm being built up of fluid of varying consistencies and qualities which may still possess the property of flowing freely

like a fluid, or have a distinct form impressed upon it in virtue of the surface tension between the cell and its surrounding medium, or between different parts of the interior of the cell.

When we enquire into the physical conditions which determine the histological characters and behaviour of living cells, the first fact which we have to take into account is that the cell and all its parts are made up of colloids. Every chemical or physical change which occurs within a cell must therefore be a change affecting colloids and take place in a colloidal medium. Without some understanding of the behaviour of this kind of material, it is impossible even to make a beginning in our task of referring vital phenomena to their causal events, or of tracing out the chain of processes intervening between the occurrence of a physical change in the environment of the organism and the physiological change in the organism itself which is its reaction to stimulus and the necessary condition of its continued existence.

The term colloid was first introduced by Graham, Professor of Chemistry in University College, London, to denote a class of bodies of which gum, dextrin, albumen and gelatin may serve as types. They are distinguished in many respects from substances such as salts, most of which can be easily obtained in crystalline form and are therefore designated crystalloids.

These colloids were shown by Graham to occur in two forms—either in a state of solution or pseudo-solution, which he designated as a *Sol* (hydro-sol, alco-sol, etc., according to the nature of the solvent), and in a solid form as a *Gel*. In this latter condition (a familiar example of which is gelatin below a certain temperature) the substance is associated, as in the sol, with a fluid such as water or alcohol; the substance *plus* solvent form however a mass apparently homogeneous, which is solid and has rigidity and elasticity.

In many cases the gel can be converted into a sol and

vice versâ by the alteration of external conditions. In other cases the change is irreversible and the gel once formed from a sol cannot be brought again into the fluid form.

Other characteristics of colloids are their extremely slight diffusibility and the fact that they are practically indiffusible through animal membranes. This latter property was utilised by Graham in the invention of the process of dialysis for freeing colloidal solutions from dissolved salts. Many of these properties suggest that the characteristics of colloids may be bound up with the large size of their molecules. Thus it is often found that, whereas the lower members of an organic series fall into the class of crystalloids, the higher members of the same series are typical colloids. Sodium acetate, for instance, with a low molecular weight, is soluble in water and diffuses with ease; sodium palmitate, with a molecule many times the size of the acetate, is soluble in water, but the solution so formed is colloidal. The soap itself is practically indiffusible, and when a solution either in water or alcohol is cooled, we get a gel similar to that formed on cooling a solution of gelatin. Nor does the existence of such simple bodies as silicic acid, ferric hydrate, or even metals themselves in the form of colloidal solution, militate against this conclusion, since we have every reason to believe that, in the colloidal state, the molecules of ferric oxide or silicic acid are no longer present as SiO_2 or Fe_2O_3, but as highly polymerised aggregates of molecules of the simpler type.

All the methods, which are at our disposal for determining the number of molecules in a solution, point to this number, in the case of the colloid solution of ferric hydrate, being many hundred times smaller than would be the case if the solution contained molecules of Fe_2O_3 or $Fe_2(OH)_6$. It is therefore not surprising, in view of the results of chemical examination of living structures, that the material of which

these are built up should be almost exclusively colloidal in nature. When we take protoplasm, *i.e.*, living material such as would be presented by the pseudopodium of myxomycetes, by lymph cells, or by liver cells, and break it up by chemical means so as to arrive at an idea of its proximate constituents, the first fact which impresses us is the enormous complexity of its chemical structure. As proximate constituents of living tissues we are accustomed to name the proteins, the fats, and the carbohydrates. The proteins, which are gradually yielding up the secret of their composition in the hands of accomplished chemists, such as Fischer, Kossel, and others, are losing in the process nothing of their imagined complexity.

In the living cell, as has been pointed out by Kossel, the proteins rarely occur in the uncombined condition. In almost all cases they are associated with other complex molecules such as nuclein, with phosphorised fats such as lecithin, and with carbohydrates or nitrogen-containing derivatives of the carbohydrates. In the case of one protein, viz., hæmoglobin, many lines of research concur in pointing to a molecular weight in the neighbourhood of 16,000. A direct determination of the osmotic pressure of the proteins of serum points to a molecular weight of about 30,000, and it seems therefore probable that the highly complex compound of nuclein, lecithin, fat, carbohydrates and protein, which form the main constituents of the cytoplasm, may have a molecular weight well over 100,000.

The size of a molecule of water has been reckoned to be about $\cdot 7 \times 10^{-7}$ mm. If the molecular diameter were proportional to the molecular weight, a molecule ten thousand times as large, *i.e.*, with a molecular weight of 180,000, would have a diameter of $\cdot 7 \times 10^{-3}$ mm. This is 0·7 μ, *i.e.*, a size within the limits of microscopic vision and transcending the particles

of many permanent suspensions. Although we have no evidence that the size of a molecule is arithmetically proportional to its molecular weight, there is no doubt that the size must be a function of the molecular weight and must increase with the latter. A molecule with a molecular weight of 100,000, although probably not directly visible with the microscope, might have a refractive index differing from the surrounding medium; like a particle of dust in the familiar Tyndall experiment it would scatter rays of light, and might therefore be rendered visible by some method of illumination such as that adopted in the ultra-microscope of Zigmondy. But such huge molecules can no longer be expected to follow exactly the laws which have been derived from the study of the behaviour of the almost perfect gases and similar substances. In these the size of a molecule under ordinary conditions is negligible compared with the distance between each molecule, so that each molecule may be regarded as a point of force. Molecules of the size we have suggested would possess the properties of matter in mass. They would have a surface of measurable extent, and their relation to the molecules of the water, or solvent surrounding them, would be determined by the laws of adsorption rather than by the laws of interaction of molecules. As a matter of fact we find that the solutions of the different colloids which make up the animal cell present an amazing mixture of properties, some of which betray them as mechanical suspensions, while others partake of the nature of chemical reactions, such as those usually dealt with by the chemist.

Let us briefly consider some of the distinguishing features of such solutions. It has been hotly debated whether a colloidal solution, or sol, is to be regarded as a solution at all, or as a suspension. The chief criterion of a true solution is its homogeneity. In a solution the molecules of the solute

are equally diffused throughout the molecules of the solvent, and it is impossible without the application of energy to separate one from the other. Thus filtration, gravitation, leave the composition of the solution unchanged. It is true that by the employment of certain kinds of membrane, *e.g.*, the semi-permeable copper ferrocyanide membrane, it is possible to separate solute from solvent, but in this case the force required to effect the filtration is enormous and grows with every increase in the strength of the solution. The increase of the force required is the osmotic pressure of the solution, and it becomes natural therefore to regard the possession of an osmotic pressure as a distinguishing criterion of a true solution. Is there any evidence that colloid solutions also display an osmotic pressure? Sabanejeff attempted to decide this question in an indirect manner, *i.e.*, by the determination of the depression of freezing-point caused by the addition to water of various colloids. The depressions observed by this author were so small that they might be regarded as falling within the limits of experimental error. Assuming that the depression in each case was due to the presence of the dissolved colloid, Sabanejeff arrived at the following molecular weights for certain colloids:—

Tannin	1,322
Egg albumen	15,000
Starch	over 30,000
Silicic acid	over 49,000

I have attempted to determine the osmotic pressure of colloidal solutions directly, taking advantage of the fact that many colloidal membranes, while permitting the passage of water and salts, are impermeable to colloids in solution.

In order to determine the osmotic pressure of the serum proteins, 150 cc. of clear filtered serum are filtered under a pressure of 30 to 40 atmospheres through a porous cell which

has been previously soaked with gelatin. At the end of twenty-four hours about 75 cc. of a clear, colourless filtrate is obtained perfectly free from all traces of protein. This filtrate has practically the same freezing point as the original serum, provided that the first ten cubic centimetres of the filtrate, which are contaminated with the water permeating the gelatin,* have been discarded. Of course the proteins contained in the serum, if they have an osmotic pressure, must

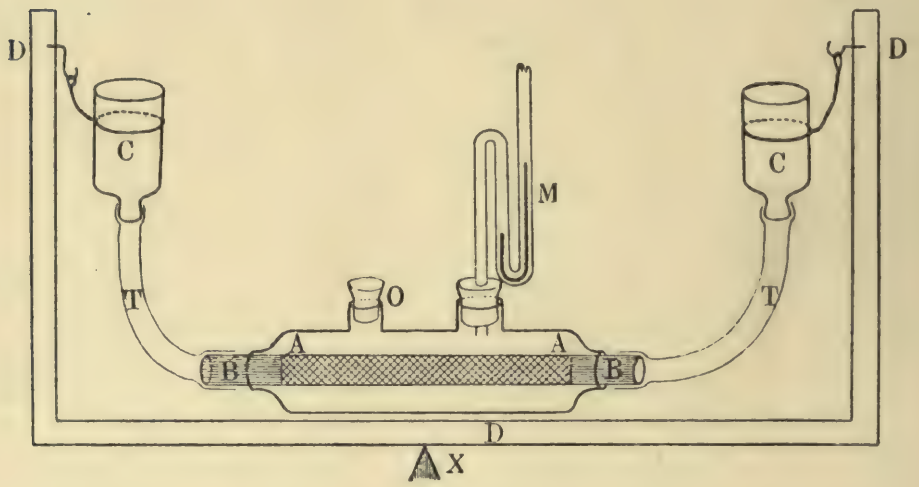

FIG. 1.

cause some depression of the freezing point, but a pressure of 45 mm. Hg. would correspond only to ·005 C., which is within the error of observation. The concentrated serum left behind in the filter is then put into the osmometer, the filtrate being used as the inner fluid.

The construction of the osmometer will be readily seen from the accompanying diagram.

The tube BB is made of silver gauze connected at each end to a tube of solid silver. Round the gauze is wrapped a piece

* The first portion of the filtrate would be more dilute than the later portions owing to the adsorption of some of its salts by the gelatin film.

of peritoneal membrane (as in making a cigarette). This is painted all over with a solution of gelatin (10 per cent.), and then a second layer of membrane applied. Fine thread is now twisted many times round the tube to prevent any disturbance of the membranes, and the whole tube is soaked for half-an-hour in a warm solution of gelatin. In this way one obtains an even layer of gelatin between two layers of peritoneal membrane, and supported by the wire gauze. This tube so prepared is placed within a wide tube AA which is provided with two tubules at the top. One of these O is for filling the outer tube, the other is fitted with a mercurial manometer M. Two small reservoirs CC are connected with the outer ends of BB by means of rubber tubes. The whole apparatus is placed in a wooden cradle DD pivoted at X and provided with a cover, so that it may be filled with fluids at different temperatures if necessary. The colloid solution is placed in AA, and the reservoirs CC and inner tube BB are filled with a salt solution approximately or absolutely isotonic with the colloid solution. The apparatus is then made to rock continuously for days or weeks by means of a water motor. (The two reservoirs CC are corked, and connected by means of a tube, in order to avoid evaporation.) In this way the fluid on the two sides of the membrane is continually renewed, and the attainment of an osmotic equilibrium facilitated.*

With this apparatus I found that the colloids in blood serum, containing from 6 to 8 per cent. proteins, had an osmotic pressure of 25 to 30 mm. Hg., which would correspond to a molecular weight of about 30,000. Using "purified" proteins, Waymouth Reid † was unable to detect any osmotic

* A more compact osmometer for similar purposes has been devised by Moore, and will be found described in the *Biochemical Journal*, II., 54, 1906.

† *Journ. of Physiol.*, Vol. XXXI., p. 438, 1904.

pressure whatever, though hæmoglobin* gave a small osmotic pressure of about 4 mm. Hg. for a 1 per cent. solution. More satisfactory results were obtained by Hüfner and Gausser.† A 5·27 per cent. solution of horse hæmoglobin gave a pressure of 58 mm. Hg. and a 10·8 per cent. solution hæmoglobin from the ox gave a pressure of 109 mm. Hg. at 10° C., corresponding to a molecular weight of 16,000. Moore has found that soaps exercise a feeble osmotic pressure. Certain colloidal solutions, such as starch or glycogen, and probably globulin, display no appreciable osmotic pressure. We must conclude that, in a hydrosol, the osmotic pressure is only small and may be entirely absent. Can we therefore divide colloidal solutions into two classes, viz., those which form true solutions and present a feeble osmotic pressure, and those which only form suspensions and therefore exert no osmotic pressure? A consideration of the behaviour of various colloidal solutions shows that such a division is not possible. In the case of inorganic colloids, such as arsenious sulphide, Picton and Linder have pointed out that all grades exist between true solutions and suspensions. With increasing aggregation of the molecules, the suspension becomes coarser and coarser until finally the sulphide separates in the form of a precipitate.

Moreover, all colloids, even those such as starch or gelatin, which are insoluble in cold water, exhibit a phenomenon, viz.: Quellung or imbibition, which in many cases it is impossible to distinguish from the process of solution. This phenomenon, which was long ago studied by Chevreul and has lately been the subject of a series of careful experiments by Overton, is exhibited by all animal tissues and all colloids. Thus elastic tissue dried *in vacuo* absorbs from a saturated solution of

* W. Reid, *Journ. of Physiol.*, Vol. XXXIII., pp. 12—19.

† Du Bois' *Archiv*, 1907, p. 209.

common salt 36·8 per cent. of water and salt. If dried colloids be suspended in a closed vessel over various solutions, they will take up water in the form of vapour from the solution, and the osmotic pressure of the solution in question will inform us as to the amount of work which would be necessary in order to separate the water again from the colloids.*

Thus it has been reckoned that to press out water from gelatin containing 28·4 parts of water to 100 parts of dried gelatin would require a pressure of over two hundred atmospheres. The imbibition pressure of colloids increases rapidly with the concentration of the colloid and at a greater rate than the latter. In this respect however, imbibition pressure resembles osmotic or indeed gaseous pressure. At extreme pressures the pressure of hydrogen rises more rapidly than its volume diminishes. In solutions this effect is more marked the larger the size of the molecule. Thus a 6·7 per cent. solution of cane sugar has the same vapour tension, and therefore the same osmotic pressure, as a ·67 per cent. NaCl solution. A 6·7 per cent. cane sugar solution has however the same osmotic pressure as an 18½ per cent. solution of common salt. It is impossible therefore to draw any hard line of distinction between imbibition pressure and osmotic pressure. In the same way it is impossible to say where a fluid ceases to be a solution and becomes a suspension. All grades are to be found between a solution such as that of common salt with a high osmotic pressure and optical homogeneity, and a solution such as that of starch, which scatters incident light and is therefore opalescent and in ordinary solution has no measurable osmotic pressure.

The close connection between the processes of imbibition and of solution is shown also by the fact that this latter process

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* Cp. Overton, *loc. cit.*, p. 796.

occurs only in certain media, the nature of the media being dependent on the chemical character of the substances in question. Thus all the crystalline carbohydrates—such as grape sugar and cane sugar—are easily soluble in water, only slightly soluble in alcohol, and practically insoluble in ether and benzol. The amorphous carbohydrates, which must be regarded as derived by a process of condensation from the crystalline carbohydrates, *e.g.*, starch, cellulose, gum arabic, etc., have a strong power of imbibition for water. This power may be limited, as in the case of cellulose, or may be unlimited, as in the case of gum arabic, so that a so-called solution results. On the other hand they swell up but slightly in alcohol, and are unaffected by ether and benzol.

In the same way proteins all take up water, and in many cases form a so-called solution, but are unaffected by ether and benzol—a behaviour which is repeated in the case of the amino-acids, out of which the proteins are built up, and which are easily soluble in water, but are practically insoluble in ether and benzol. On the other hand, indiarubber and the various resins take up ether, benzol and turpentine often to an indefinite extent, while they are untouched by water. With this behaviour we may compare the easy solubility of the hydrocarbons, the aromatic acids and esters in ether and benzol, and their insolubility in water. As Overton has pointed out, the power of amorphous carbohydrates to take up fluids is modified by alteration of their chemical structure in the same direction as the solubility of the corresponding crystalline carbohydrates. Thus, if the hydroxyl groups in the sugars be replaced by nitro, acetyl or benzoyl groups, they become less soluble in water, while their solubility in alcohol, acetone, etc., is increased. In the same way the replacement of the hydroxyl groups in cellulose by NO_2 groups diminishes the power possessed by this substance of taking up water, but

renders it capable of swelling up or dissolving in alcohol and acetone.

Instability of Colloidal Solutions.—It is probably to the relatively large size of the molecules or particles of which they are composed, that we must refer the unstable character of most colloidal solutions. The colloid can be precipitated in association with a certain amount of the solvent, or the whole mass can be turned into a gel by very various means, such as the addition of electrolytes, by heating or mechanical agitation, or by the addition of some other colloid. In this precipitation an important part is played by the fact that colloidal particles, like the ions in a solution of sodium chloride, in many cases carry electric charges. The mutual repulsion of the particles thus brought about helps to keep them in suspension. If they are robbed of their charge by addition of an electrolyte, by the passage of a current, or by the addition of an oppositely charged colloid, this mutual repulsion is done away with, the particles aggregate and fall to the bottom as a precipitate. It must be remembered that, even when precipitation has been brought about by one of these means, the association between the colloid and water has not been destroyed, but the precipitate still contains a large amount of imbibed water, which can be removed only by the application of a considerable force. The essence of the change which has taken place consists in the conversion of a colloid with unlimited powers of swelling in water into a colloid whose powers of imbibition are limited, as is the case with an animal material such as white fibrous tissue.

Surface Phenomena of Colloidal Particles.—The great size of the molecules or molecular aggregates, which are present in colloidal solutions, justifies us in ascribing to them definite surfaces and therefore properties which are associated with any surface. The distribution of a substance within a fluid

as a rule is not the same as its distribution on the free surface of the fluid. Thus, if a dissolved substance diminishes the surface tension of the fluid it will tend to accumulate at the surface in greater concentration than in the interior of the fluid. Moreover, in contact with a surface, the pressure either of gases or of vapours tends to be diminished, and it is probable that the same rule applies to many dissolved substances. Thus it is impossible to get rid of the last traces of air from a vessel by one evacuation. The air adheres with such tenacity to the superficial layer of the glass that repeated heating and evacuation are necessary in order to remove the last traces. This power possessed by surfaces of diminishing gas or vapour tension, and therefore of condensing substances on themselves, is spoken of as adsorption. In a sol the surface of the particles must be enormous in proportion to their total mass. This will be evident if we consider the effects of minute subdivision in increasing surface. A sphere of 10 ccm. would have a surface of 22 sq. cm. If the sphere were reduced to a fine powder, consisting of spherules, each of which was 0·00000025 cm. in diameter, the total surface of the solid would amount to 20,000,000 sq. cm., *i.e.*, nearly half an acre. At the whole of this surface adsorption may take place, involving the concentration of electrolytes or gases. The behaviour of each particle will thus be determined, not only by its own nature, but also by that of the little court of adsorbed material by which it is surrounded. So great is this power of adsorption that it is practically impossible to get rid of the last traces of ash, *i.e.*, adsorbed electrolyte, from a gel by physical means, such as washing with distilled water.

This power of adsorption is not however indiscriminate. It is determined, not only by the extent of surface afforded by the particles, but also by the chemical nature of the particles

themselves. This is shown by the varying affinity for dye-stuffs of substances of different chemical composition, and may be illustrated by the behaviour of the colloids which play an important part in the building-up of the animal cell. Thus, as Hardy has pointed out, the globulin of blood serum may occur in four different states, viz., globulin itself, compounds of globulin with acid or with alkali, and compounds of globulin with neutral salts. The amount of acid or alkali combining with the globulin is indeterminate, the effect of adding either acid or alkali to the neutral globulin being to cause a gradual conversion of an opaque milky suspension into a limpid, transparent solution. On drying HCl globulin the dried solid is found to contain all the chlorine of the HCl used to dissolve it. The acid must therefore be regarded as being in true combination. Both acid and alkali globulins act as electrolytes, and the globulin, being electrically charged, takes part in the transport of electricity. In order to produce the same extent of solution, the concentration of alkali added must be double that of the acid. The relation of globulin to acids and alkalies is similar to that of the so-called amphoteric substances, such as the amino-acids. An amino-acid such as glycin can react as a basic anhydride with other acids, thus:—

$$\begin{matrix} NH_2 \\ CH_2 \\ CO{\cdot}OH \end{matrix} + HCl = \begin{matrix} NH_2 - HCl \\ CH_2 \\ CO{\cdot}OH \end{matrix}$$

or as an acid anhydride with bases. Like these too, globulin forms soluble compounds with neutral salts.

From true electrolytes, colloidal solutions differ in the fact that their particles are of varying size according to the condition in which they exist, and carry varying charges of electricity, whereas an ion, such as Na′ or Cl′, has a mass which is constant for the ion in question, and always carries

the same electric charge. The charged particles of an acid or alkali-globulin may be distinguished therefore as pseud-ions.

In these adsorption combinations, although the chemical nature of the colloidal molecules is concerned, there is an absence of definite equilibrium points, such as we are accustomed to find in most chemical reactions. The inertia of the system and the large size of the molecules determine the occurrence of false equilibria and of delayed reaction. Thus the condition and behaviour of a colloidal system at any moment are determined, not entirely by the quantitative relations of its components, but also by the past history of the system. On account of this inertia, any change in a colloidal system will tend to become indefinitely slow, *i.e.*, practically to cease, before complete equilibrium is attained. Any system of this nature, with which we may have to deal, may be regarded as in a condition of stress, the direction of the stress being determined by that of the transformation to which the system was last subjected. Such a system has what we might loosely speak of as memory—a memory which would favour the continuance of an antecedent process, and oppose the occurrence of a process in the reverse direction. In order to destroy a configuration that is once established we have, in consequence of the inertia of the system, to overstep widely the conditions of its formation. Thus a 10 per cent. solution of gelatin sets at 21° C. but does not melt until warmed to 29·6° C. Solutions of agar in water set at about 35° C. but do not melt under 90° C. A gel of gelatin takes twenty-four hours after setting before it attains a constant melting point.

Surface Phenomena of Colloidal Solutions (*Sols*).—A gel differs from an ordinary solid in that it is freely permeable by water and by most dissolved crystalloids. Sodium chloride diffuses with practically the same rapidity through a gel

composed of 5 per cent. gelatin as through pure water. So far as concerns, however, the particles or molecules of the colloid responsible for the formation of the gel, this resembles an ordinary solid in that the molecules are constrained to occupy a particular position and are not free to move within the gel.

In a sol, on the other hand, the colloidal particles are freely moveable among themselves, though, in consequence of their great size and inertia, any movement determined by differences in concentration will occur at an infinitely slower rate than is the case with smaller molecules, such as NaCl.

I have already mentioned that any fluid at its surface possesses different qualities to those possessed by it in its interior, and that, for instance, any dissolved substance which diminishes the surface tension of the solvent tends to accumulate in greater concentration at the surface. Almost all colloids with which we are acquainted possess this property of diminishing surface tension, and on this account tend to accumulate in greater concentration at the surface. Owing to the enormous size of the colloidal molecules, a considerable increase of concentration is not possible without bringing the particles within each other's sphere of influence, so that they may be regarded as actually touching. We thus get formed at the surface of the hydrosol—such as one of albumen—an actual solid pellicle or gel composed of egg-albumen. Every fluid mass of colloid in the body will tend at its surface to become coated with such a gel or pellicle, which will resist deformation and extension and the properties of which will determine the access of fluids or solids to the hydro-sol within.

Although we have spoken of protoplasm as essentially fluid and composed of different hydrosols of varying complexity, it is evident that each mass of protoplasm will present solid

or gel pellicles at its periphery, as well as at any part in its interior where chemical differences determine the production of a surface with a definite surface tension. By the greater or less formation of such pellicles we may explain the varying rigidity of different forms of living tissue and the varying accessibility or permeability of different cells to the entrance or passage of the different constituents of their surrounding medium.

In this way chemical, physical, and structural organisation will go hand in hand. Every cell may be looked upon as formed of one or more molecules of extreme complexity in which proteins, fats, phosphorised fats, and carbohydrates are bound together in one immense complex, so large, in fact, that it may present different chemical reactions according to the situation at which any reaction is excited. The varying chemical structure at different parts of this molecule will determine a behaviour of the whole molecule, or molecules, constituting the cell, which will be conditioned by spatial relationships. In consequence of the heterogeneous character of the molecule, substances will be produced in different parts of the cell which are immiscible with the surrounding fluid, and will therefore become separated off by colloidal pellicles; and the nature of these films will determine the subsequent relations between the secretory vacuole and the surrounding protoplasm.

A study of the chemistry of the cell enables us therefore to form a conception of the manner in which its varying behaviour, according to the nature of the environment, is brought about; since the relation of the cell to its environment, as well as the inter-relation of its parts among themselves, must depend on the qualities of the pellicles bounding the surfaces of separation.

It may be interesting at this point to consider shortly the

main features which determine the qualities of such a membrane and the transference across it of various substances in solution. In my next lecture I shall have to deal with the effects of this bounding membrane, or '*Plasmahaut*,' on the interchanges between the cell and the surrounding medium, as determined by experiments on living cells. In our physical experiments it is not easy to reproduce such a membrane of molecular dimensions. There is no reason, however, to believe that the results of experiment on thicker membranes differ essentially in any other respects than in time-relations from the phenomena which would be presented if their thickness were reduced to that of a single molecule. The transference across any colloidal membrane depends on its permeability, that is to say, on the substances which it will allow to pass. The permeability of such membranes to any given substance is apparently conditioned by the solubility of the substances in the membrane, or of the membrane in the substance. Under the term solubility we may include also the property of imbibition, or '*Quellung*.' As we have already seen, these qualities are determined in their turn by the chemical nature of the substances in question. The carbohydrates, for instance, are either soluble in or imbibe water; the resins and allied substances, such as india-rubber, vulcanite, etc., will take up ether and sometimes alcohol, but are practically unaffected in the presence of water, just as the hydrocarbons are soluble in ether but insoluble in water.

The same contrast is seen when we compare the permeability of these substances. A colloidal membrane composed of protein or gelatin, or allied substances, is easily permeable by water as well as by substances dissolved in water, such as salt and sugar. It is less permeable to ether and practically impermeable to substances such as benzol or hydrocarbons, or fats. On the other hand, a disc of india-rubber or vulcanite

allows no water to pass, but is easily permeable to ether or benzol. Thus if two closed vessels, containing ether and alcohol respectively and connected with manometers, be separated by a disc, the passage of fluid will depend on the nature of the disc. If the disc be of vulcanite, ether passes into the alcohol and causes a great development of osmotic pressure on the alcohol side. If however the disc be of moist animal membrane—such as pig's bladder—the passage is in the opposite direction, viz., of alcohol into ether, and the development of pressure is on the side of the ether. We shall later have occasion to illustrate this dependence of permeability on chemical relationships between the membrane and the dissolved substances.

Another important quality of these surface pellicles, which will play the greater part the more microscopic the dimensions involved, is their surface tension. The effect of surface tension may be regarded as equivalent to a contracting force, the surface continually striving to attain its smallest possible area, just as an inflated india-rubber ball tends to collapse in consequence of the tension of the rubber membrane. With ordinary drops or masses of fluid, the effect of this surface tension on the pressure in the interior of the fluid is practically negligible. The actual pressure exerted will however vary inversely as the dimensions of the mass. Thus in a sphere where P is the pressure, A is a constant depending on the nature of the fluids in contact, and R is the radius of the sphere, the pressure would be given by the following equation: $P = \frac{2A}{R}$. The smaller the drop therefore, the greater the pressure. In very minute drops the pressure might well amount to several atmospheres.

This pressure might be of considerable importance in determining the relations between the contents of the minute

vacuoles, which occur to such a large extent in secreting cells, and the surrounding protoplasm. If a substance were present both within and without the vacuole, to which the pellicle bounding the vacuole was impermeable, it is evident that a great hydrostatic pressure within the vacuole determined by the surface tension might give rise to important differences of concentration within and without the vacuole. It is possible that this factor might play a part in determining the marked differences of concentration which are found to exist between the blood and the product of secretion of many glands, differences which involve work on the part of the cells, and therefore the existence of a 'machine' with the mechanism of which we are at present entirely unacquainted.

Surface tension must also determine the form of any cell or any part of a cell. The surface tension between a cell and its surrounding medium, *e.g.*, water, depends, as we know, entirely on the chemical nature of the surface. Alter this surface in the slightest degree, as, *e.g.*, by the deposition of a few ions of one charge or another, and we at once alter the surface tension between the cell and its surroundings, and with this also the electrical conditions of the surface.

In recent times MacDonald has shown how such minute changes of concentration at the surface of the nerve fibrils may possibly account for the propagation of a nerve impulse as a result of local disturbances or excitation. At the present time I want especially to call your attention to the fact that a slight chemical change limited to part of a spherical cell will alter the surface tension at this spot. If the surface tension is increased, the pellicle will contract and may cause a depression in the neighbouring part of the cell. If on the other hand the surface tension be diminished, the effect will be the same as the sudden thinning of a small part of the wall of a rubber balloon. The tension of the rest of the wall causes the

contents of the balloon to bulge out through the thinner portion of the wall. An analogous change occurring in the boundary layer of an amœba will bring about the protrusion of a pseudopodium. If we assume with Bernstein that in its ultimate structure a muscle consists of chains of oval particles, whose form is determined by the constraining effect of an elastic pressure on a fluid sphere with a high surface tension, it is evident that any chemical change, which will increase this tension, will cause the particles to approach more nearly to a spherical form, and thus bring about a thickening and shortening of the whole muscle. The energy of a muscular contraction would thus be, in the last instance, referable to the energy of surface tension.

I hope to have shown you in this lecture that our knowledge of the properties of colloidal solutions, in which water forms so essential a part, although still so limited, enables us nevertheless to form a conception of the mechanism underlying many of the phenomena which we regard as distinctive of living organisms.

LECTURE II

THE OSMOTIC RELATIONSHIPS OF CELLS

In my last lecture I drew your attention to the marked difference which is found to exist between the elementary composition of living organisms, and that of the medium in which they live, and to the fact that similar differences are found when we compare the cells forming part of a complex organism, such as man, with the internal media, such as blood, with which they are continually in contact.

The composition of any cell is something peculiar to itself. Regarding as we do the variability in the reactions of different kinds of organisms or of cells as conditioned by the chemical structure of their protoplasm, it is only natural that the differences in the chemical compositions of different organisms are almost as marked as those ruling between the organisms and their surrounding dead medium. These reactions involve the necessity of each cell being cut off, so to speak, from its environment. In maintaining this privacy of cell life, the surface layer of protoplasm must play an all-important part. Since it is by means of this layer that the organism enters into relation with its environment, it acquires a prime importance to the life of the cell, and much labour has been devoted to the experimental investigation of the properties of the superficial layer of the protoplasm, or *Plasmahaut*.

This layer is not to be confounded with the cell-wall. The latter, which plays a great part in the building up of vegetable tissues, is formed by a process of secretion from the living protoplasm and is situated altogether outside the

superficial Plasmahaut. The cell-wall differs considerably in its chemical composition from the protoplasm out of which it has been formed. In most plants it consists of cellulose, a substance belonging to the carbohydrate group, and with a composition represented by some multiple of the formula $C_6H_{10}O_5$. In other cases the cell-wall may be built up from calcium carbonate or other lime salts, from silica or from chitin, and may be perforated to allow the passage of communicating strands of protoplasm between adjacent cells. It is often freely permeable to all kinds of solutions, and does not in this case play any part in regulating the interchanges of the cell with its environment.

The superficial layer of protoplasm represents that part of the living substance which stands in immediate relationship to the environment. Every change in the latter can influence the living cell only through this layer, by which also substances must pass on their way into the cell for assimilation, or out of the cell for excretion. The retention of individuality by the cell must be determined by chemical and physical differences between this layer and the surrounding fluid. Since it differs from the rest of the protoplasm in the changes to which it is subject, it must also differ in its chemical composition, apart altogether from the factors which, as we saw above, determine molecular differences between the surface and the internal parts of any colloidal solution. On this account we must assume the existence of a definite boundary layer even when under the highest powers of the microscope we can perceive no differentiation between this layer and the deeper parts.

A cell which leads its life in a fluid environment must take up the greater part of its food material from this medium in the form of solution, the passage of food substances from the medium into the body of the cell being

determined by the permeability of the superficial protoplasm. The immiscibility of the protoplasm with the surrounding fluid shows that the permeability of the membrane must be a limited one. The qualitative permeability can be easily studied in vegetable cells. These present within a cellulose wall a thin layer of protoplasm (the primordial utricle), enclosing a cell sap. If the root hairs of Tradescantia be immersed in a 10 per cent. solution of glucose or in a 2 to 3 per cent. solution of salt, a process of *plasmolysis* takes place. The cell sap diminishes in amount by the diffusion of water outwards, so that the primordial utricle shrinks. On immersing the cells in distilled water, water passes *into* the cell sap in increasing amount until the further expansion of the protoplasmic layer is prevented by the tension of the surrounding cell-walls. This behaviour can only be explained on the assumption that the protoplasm is impermeable both to sugar and to salt, but is freely permeable to molecules of water, *i.e.*, it behaves as a ' semi-permeable ' membrane. Similar experiments can be made on animal cells. The most convenient for this purpose are the red blood corpuscles. These also shrink when immersed in salt solution with a greater molecular concentration than would correspond to the plasma of the blood from which the corpuscles are derived ; whereas, if placed in weak salt solution or distilled water, they swell up and burst, discharging their hæmoglobin in solution into the surrounding fluid. By comparison of various salts it is found that the strength of each salt solution which is just necessary to cause plasmolysis, or hæmolysis as the case may be, is determined entirely by its molecular concentration, *i.e.*, a decinormal solution of sodium chloride will be equivalent in its effects on the cells to a decinormal solution of potassium nitrate or of sodium sulphate. This impermeability of the plasma skin does not apply to all dissolved substances. Thus Overton

has found that, whereas this layer is practically impermeable to salts, hexoses, and amino-acids, it permits the easy passage of monatomic alcohols, aldehydes, alkaloids, etc. All these substances are more soluble in ether, oil, and similar media than they are in water. The passage of dissolved substances through a medium wetted by the solvent depends on the solubility of these substances in the membrane, and Overton therefore concludes that the superficial layer of protoplasmic cells must itself partake of a 'lipoid' character, and that cholesterin and lecithin probably enter largely into its composition. Thus only those dyes which are soluble in a mixture of melted lecithin and cholesterin have the property of penetrating the living cell, and it is only these dyes, such as methylene blue, neutral red, etc., which can be used for *intra vitam* staining. For the same reason substances which have the power of dissolving lecithin and cholesterin, such as ether or bile salts, also act as hæmolytic agents, *i.e.*, they cause a destruction of the red blood cells by dissolving the superficial layer which is necessary for their preservation from the solvent effects of the surrounding fluid.

These results seem at first to land us in difficulty. Since the superficial layer of the protoplasm is impermeable, so far as our experimental results go, to the greater number of dissolved salts, one might expect that the cells would be indifferent to the qualitative composition of the medium and would be affected only by its qualitative composition, *i.e.*, by the total osmotic pressure of the surrounding fluid. This is far from being the case.

It was shown long ago in Ludwig's laboratory that the inorganic constituents of blood serum played an important part in determining the heart-beat, and Ringer taught us to discriminate between the physiological effects of calcium, potassium, and sodium salts and to assign to each of these

salts a specific action in the regulation of the cardiac activity. Whereas we can inject litres of sodium chloride solution into an animal's vein without ill effects, a few cubic centimetres of solution of potassium chloride will bring about death by failure of the heart. The same sensitiveness of the animal cell to qualitative differences in the composition of the surrounding medium is shown in some interesting observations of Loeb * on the conditions of survival of a marine crustacean, Gammarus, found in the Bay of San Francisco. Loeb pointed out that when Gammarus was transferred from bay-water into distilled water, respiratory movements stopped in about half-an-hour and the stoppage was permanent unless the animal was replaced in the sea-water within about ten minutes. If the Gammarus were put into a solution of cane sugar in distilled water of a concentration isosmotic with sea-water, it died as rapidly as in distilled water, and the same thing happened when the animals were placed in pure NaCl solution isosmotic with sea-water. They died still more rapidly when they were put into a solution containing all the salts of the sea-water, and in the same proportion, with the exception of sodium chloride. In solutions containing NaCl, KCl and $CaCl_2$ in the proper proportion, the animals lived as long as 48 hours, and if a little $MgCl_2$ were then added, the animals survived as long as in the ordinary sea-water.

We see therefore that not only must the medium surrounding a cell organism have a definite osmotic pressure, but that this pressure must be supplied by specific salts.

Are we to conclude from these facts that the observations previously mentioned on the permeability of the Plasmahaut were wrong, and that the Plasmahaut is really permeable to all these salts, but that the passage is so slow that it is not

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* J. Loeb. "The Dynamics of Living Matter," p. 46. 1906.

detectable by our grosser means of analysis? I believe such a conclusion would not really be warranted. In the first place it is important to remember that the phenomena which we associate with life are most of them reactions to stimuli. Every stimulus affects in the first place the surface layer, and we have seen that many of the reactions are also determined by changes in this layer. Its surface tension is a function of its composition, and therefore, among other factors, of the salts which are adsorbed by the surface. It would be quite comprehensible that, even though the salts do not penetrate into the interior of the cell, variations in the composition of the medium would alter the surface, and thus interfere with or annul the reactions, such as contractility, the transference of gas, or the assimilation of food, which we associate with the possession of life.

Such an explanation will not suffice to explain all the facts. Dextrose, to which the Plasmahaut is apparently impermeable, can yet serve as a very efficient food for the cell, and must therefore be taken up by the latter. Overton has shown that, although impermeable to sugar, the superficial cell layer is easily traversed by methyl derivatives of the sugars. There is no doubt that the relative solubilities of the absorbed substances in the cell and its surroundings respectively must play a part in the process of assimilation, at any rate by lowly organised cells, and still more in the intracellular exchanges involved in the processes of secretion and excretion. When a watery solution of iodine is shaken up with chloroform, the latter sinks to the bottom, carrying with it the greater part of the iodine. If a watery solution of an organic acid, such as lactic, be shaken with ether, the latter fluid will extract the greater quantity of the acid. In no case will the extraction be complete, but there will be a definite ratio between the amount dissolved by the ether and the amount dissolved by

the water, the so-called 'coefficient of partage' depending on the variable solubilities of the dissolved substance in the two menstrua. In the same way a mass of protoplasm will tend to absorb from the surrounding medium and to concentrate in itself all those substances which are more soluble in the colloidal system of the protoplasm than in the surrounding fluid. This process of absorption may be carried to a very large extent if the dissolved substances meet in the cell with any products of protoplasmic activity with which they may form insoluble compounds, since they are thereby removed from the seat of action. By such a process as this we may account for the accumulation of calcium or silicon in large quantities in connection with the bodies of various minute organisms.

It is possible that in the process of absorption some chemical change in the sugar might take place, which would render it more soluble in the surface layer of the protoplasm. The sugar, for instance, might be built up with lecithin to form some lipoid-soluble compound to which the Plasmahaut would be permeable. But this change must be accomplished by the superficial layer itself. We arrive thus at the conclusion that the Plasmahaut, though behaving like a dead lipoid membrane, such as can be made by soaking silk with a solution of lecithin and cholesterin, is yet in reality part and parcel of the living protoplasm of the cell, taking part in its changes and absorbing any substance which is required by the cell at the moment, *i.e.*, for which combining affinities have been set free in the cell. The physical permeability of the cell-skin is a necessary condition for the privacy of the cell-metabolism; but it does not prevent the cell taking up from the surrounding medium any constituent which is lacking to restore the constitution of the protoplasm to the normal.

Nearly all animal and vegetable cells allow the free passage of water through their surface layer. Hence in animal cells,

the osmotic pressure of the cell-contents is in most cases identical with that of the surrounding medium. Laked blood, for instance, in which the red blood corpuscles are broken up and their contents freely mixed with the serum, has the same osmotic pressure, as judged by the depression of the freezing point, as the serum from the original blood. Any change therefore in the molecular concentration of the surrounding fluid has, as its first effect, an increase or diminution in the size of the cell, which takes or gives up water until the osmotic pressure of its contents is once more equal to that of the medium in which it is immersed. Where this equality does not obtain and the osmotic pressure of the cell-contents is greater than that of the surrounding medium, a rigid cell-wall is necessary in order to prevent the swelling of the cell and the equalisation of its pressure to that of its surroundings. This is the case with nearly all vegetable cells. In these, when growing, the cell-contents have a molecular concentration equal to that of a solution of 1 to 1·5 per cent. KNO_3, *i.e.*, a concentration not far removed from that of most animal cells and fluids.

The result of this concentration, which is found both in land and water plants, is that the cell-contents exert a considerable pressure on the superficial layer of protoplasm and through this on the cell-wall. The whole plant is thus in a condition of turgor—a condition which not only maintains the rigidity of the structure, but is necessary if the process of growth by intussusception is to take place. This uniform, moderate osmotic pressure applies only to the actively growing parts of the plants. In cells which are the seat of deposition of soluble store-materials, such as sugar (I may instance the cells of the beetroot), the pressure may be many times this amount, and in certain moulds grown on concentrated sugar solutions the osmotic pressure may be as high as 150 atmospheres.

In plant cells, with their firm cellulose walls, small changes in the molecular concentration of the surrounding medium need not cause any ill effects, apart from temporary modifications in the condition of turgor. Animal cells, on the other hand, must be extremely susceptible to any such changes. The varying concentration of the medium in which they are immersed must bring about a continual and corresponding variation in size and content in water of the cell. Moreover, their protoplasm is directly exposed to the influence of the slight qualitative changes in the environment which, as we have seen, exert such wide-reaching influences on all the cell functions.

A great step in evolution was taken therefore, when the organism secured for the majority of its cells a medium of uniform composition, by the formation of a body-cavity or cœlom, and the enclosing in this cavity of a fluid not differing widely at first from the surrounding sea-water. This step was typical of the whole course of the evolution which results in rise of type. Even at the present time the position of a man among his fellows, or of a man among other animals, is indicated by the extent to which he is able to create his environment and to keep it adapted to his special needs, so that he may never experience directly the numerous adverse influences which are present just outside his own self-created circle. Every slight deviation of an ocean current, every spell of cold weather, brings about the sacrifice of myriads of living beings, which are unable to withstand the trifling changes of saline concentration or temperature thereby induced in their surroundings. The evolution of a cœlom was followed by the appearance of circulatory and other organs designed to maintain the composition of the internal medium constant at all parts of the organism under varying internal conditions. In the highest vertebrata, the evolution of a

thermotaxic mechanism has provided for the maintenance of a constant temperature in this medium, whatever may be that of the surroundings, and in ourselves practically all the day's energies are devoted to the fashioning of an environment independent of climatic influences, and fitted in every way to maintain our functional capacities at their highest possible level: in other words, to make life worth living.

I have stated above that the internal medium of higher animals, the cœlomic fluid, representing blood, lymph, and tissue fluid in ourselves, was probably at its first appearance simply an enclosed portion of the surrounding medium or sea-water. Apart from the morphological evidence in favour of this statement, we have striking confirmation in the saline constitution of the lymph and blood-plasma of the highest animals. The three elements, sodium, potassium, and calcium, are in proportions very much like those which now obtain in sea-water. The main differences between the saline constituents of our blood-plasma and those of sea-water are (1) the greater total concentration of sea-water; (2) the greater proportion of magnesium in the latter.

In an interesting essay published by Macallum * in 1904, the reasons for these analogies and differences between blood-plasma and sea-water are set out and discussed. He comes to the conclusion that the present composition of our blood-plasma is probably identical with that of the sea-water just before the Cambrian period, when animals possessing a cœlom first made their appearance, and that it has been transmitted by heredity through the countless ages that have elapsed since that far-off period. At that time the sea-water must have been

* "The Palæochemistry of the Ocean in Relation to Animal and Vegetable Protoplasm." *Trans. of the Canadian Institute*, 1903-04.

much less concentrated than it is at present, since the constant carrying of the saline constituents of the soil by the rivers to the sea, and the removal of water from the latter by evaporation, must tend to cause a steady increase in the saline concentration of the ocean water.

In this essay Macallum also attempts to account for the marked difference between the constitution of animal cells and that of their surrounding internal medium. The beginnings of life must be placed far back in the pre-Cambrian period. Millions of years may have elapsed before the evolving protoplasm or protoplasms attained the complexity of type which is now common to every cell whether animal or vegetable. The universality of this type shows that both animal and vegetable cells must be derived from a single type which existed in the first dawnings of life on the globe and which pushed aside all the other infinite varieties of reacting protoplasm which may, and indeed must, have come into existence at one time or other during the history of this globe. In this single-celled organism was elaborated the whole process of nuclear division with its peculiar morphological features, which have continued almost unchanged through an infinity of generations animal and vegetable. "If now," Macallum asks, "heredity is so powerful in regard to structure, is it a negligible force in regard to chemical composition?" In answer to this query, he suggests that the proportions of saline constituents found in protoplasm may conceivably represent those of the salts in the primeval ocean in which life probably first made its appearance.

The proportions of potassium, calcium, sodium, and magnesium in living protoplasm are not yet known, since protoplasm has the power of precipitating these salts as inert compounds in itself or in its cell-wall. It is certain however that the proportions both of potassium and calcium to sodium

in living protoplasm are much higher than is the case either in sea-water or in the cœlomic fluid, or in the lymph or blood of higher animals. When we examine the composition of the lakes and rivers which derive their water from areas in which pre-Cambrian formations predominate, we find a corresponding excess of calcium and potassium over sodium, as compared with sea-water. Thus in the lakes of the Bavarian highlands the amount of potassium is twice that of the sodium. The calcium is in nearly all cases very abundant, and in fact forms the chief saline constituent of the water.

At the first formation of an ocean basin, which occurred in consequence of the gradual cooling of the earth's surface, and the condensation of the water previously present in the atmosphere in the form of vapour, the condensing water would decompose the hot rocky crust and wash out the soluble products of decomposition. The condensation of superheated water would convert the chlorides of magnesium, iron, and aluminium into magnesia, ferric oxide and alumina, all of which are practically insoluble; while the other chlorides, viz., sodium, potassium and calcium, would be dissolved out of the rock in amounts depending on their relative solubility. The chief saline constituent of the water flowing into the ocean basin would be these chlorides, calcium chloride being largest in amount, while potassium chloride would be more abundant than the corresponding sodium compound.

If protoplasm was formed at this time from some polymerising organic compound in the sea-water, it is readily to be comprehended that it should contain saline constituents corresponding in proportion and amount to those of the surrounding sea-water. The fundamental condition of all life and of the formation of living from dead material is segregation and reproduction by division, so that the proportion of salts, once established in a successful type, would tend to

continue with but slight modifications through the millions of years which have since elapsed. The saline constituents of protoplasm would therefore not partake of the continuous change which has since been effected in the composition of sea-water. In the latter the continual access of carbonates, and later the active intervention of living organisms, have tended to remove a large amount of the calcium and cast it to the bottom of the sea to form the masses of limestone and chalk, which are now so conspicuous an element in the earth's crust. In the same way the potassium fixed first by the living elements has been thrown down in combination with the silicates of alumina in the form of clay, so that finally the present composition of the sea has been arrived at, in which sodium chloride predominates over all the other constituents.

Whatever the origin of the cœlomic fluid, it represents now in higher animals the internal medium for all the cells of the body. In order that these may be shielded from the stress of circumstances and enabled to devote their whole energies to the special function for which they have been differentiated, the organism must be provided with distinct mechanisms for the regulation of the amount, the composition, and the molecular concentration of this fluid. This office is subserved by a variety of organs. Excess of water or salts or effete material, the products of the activity of the cells, are eliminated largely by the agency of the kidneys. In many animals there is also loss from the surface of the body and from the internal surface of the lungs. This loss both of water and salts has to be made up by the agency of the alimentary canal, *i.e.*, from without. In the higher animals the cœlomic fluid is divided into several categories, that circulating within the blood-vessels, that subject to a slow current in the lymphatic channels, and the more or less stationary fluid which bathes every cell of the body. It is this last, viz., the tissue fluid, which is

the most important for the vital activity of the body as a whole.

I propose in the following lectures to describe some of the mechanisms by which the composition and amount of this internal medium of the body are regulated, and to discuss the physical forces, intra- and extra- cellular, involved in their work.

LECTURE III

THE INTAKE OF FLUID

In all the higher animals the cells, of which their bodies are composed, are bathed by an internal medium, from which the cells derive their nourishment, and into which they discharge their waste products. By the provision of such an internal medium, the cells obtain an average constancy of environment and are withdrawn from the buffeting and constant changes to which the animal as a whole is exposed. They are thus enabled to devote their entire energies to the discharge of their particular functions in the commonwealth of the body. By this means moreover provision is made for maintaining the solidarity of the component parts of the commonwealth. The products of any one set of cells are able to influence the activity of the cells in remote parts of the body, and in some cases it has been shown that special chemical messengers are poured out into the tissue fluids for the express purpose of effecting this chemical integration and of bringing about, in widely diverse tissues, the united action to a common end which is characteristic of all the higher types of living organisms.

Constancy of medium is not secured however simply by the enclosure of a certain amount of sea-water in the body cavity. Every cell is continuously engaged in taking up food substances from the internal medium and in discharging waste products into it. In order that the organism may maintain a certain average composition of its body fluids and thus really create the environment of its constituent cells, it must be

provided with organs, or sets of cells, especially differentiated for maintaining the average composition of this fluid, either by taking up food substances from the surrounding medium, by the transformation of these foodstuffs, or by discharging into the surrounding medium the substances which would tend to accumulate in the body fluids as the result of the metabolism of the cells of the body.

This process of excretion is in nearly all animals associated with a loss of fluid, *i.e.*, of water, to the organism. Of the metabolites produced as the result of chemical changes in the tissues, some, such as CO_2, are gaseous, and in the higher animals are excreted through the lungs. Others, such as urea, are solids, and can be got rid of only in solution, so that when they leave the body they take with them a certain amount of water as well as of salts. Moreover, in animals living on the earth's surface, evaporation is constantly going on at the surface of the body, and in man this evaporation plays a prominent part in the regulation of the body temperature, *i.e.*, in creating a constant *temperature* environment for the cells of the body.

In the cell processes associated with activity there is a breaking down of complex molecules into a number of much smaller and simpler molecules. This would bring about an increase in the molecular concentration of the body fluids, were it not that any excess in the soluble substances in these fluids is eliminated in a concentrated form by the chief excretory organs, viz., the kidneys.

In these lectures we shall not concern ourselves with the maintenance of the food supply to the cells, nor to any large extent with the removal of the waste products, but shall devote our attention almost exclusively to the changes in the water content and in the total volume of the fluids of the body, and with the manner in which the alimentary canal and kidneys interact for the maintenance of normal conditions.

The intake of water, and probably of salts, by the alimentary canal, in accordance with the requirements of the organism as a whole, seems to be regulated almost entirely by the central nervous system, the higher parts of this system, viz., those concerned with appetite, being particularly involved in the process. Thus in man any large loss of fluid, as by sweating, diarrhœa, or hæmorrhage, gives rise to an intense thirst that has its natural reaction in increased intake of water by the mouth. On the other hand the property possessed by the alimentary canal of absorbing water and weak saline fluids contained in its interior is very little influenced by the state of depletion, or otherwise, of the water depôts of the body. Our own experience tells us that it is practically impossible, however large the quantities of fluid that we ingest, to bring about the production of fluid motions, and that the whole of the ingested fluid is absorbed on its way through the alimentary canal.

Thus a man may keep himself in perfect health and maintain the water contents of his body constant whether he take two pints or twelve pints of water daily. The whole process of regulation, apart from that determined by appetite, appears to be carried out at the other end of the cycle, viz., by the kidneys. As concerns absorption of water there is no chemical solidarity between the alimentary surface and the rest of the body. Whenever water is presented to the surface it is absorbed and passes into the circulation.

The case is different if large quantities of concentrated saline fluid be ingested, especially if the salts be other than sodium chloride. Certain groups of salts present greater resistance to absorption than others ; among them we may mention the tartrates and the sulphates, and it is among these, therefore, that our chief saline purgatives are found. But in every case absorption by the alimentary surface is a question of the local conditions rather than of the needs of the organism as a whole.

Only in extreme hydræmic plethora, when the intestinal wall is swollen with exuded fluid, may we observe a distinct hindering of the process of absorption or actual conversion of absorption into secretion. Such a condition of hydræmic plethora, as is produced in animal experiments by the injection of huge quantities of normal solution into the circulation, probably never occurs in the normal intact animal.

In this lecture we have to discuss the nature of the local conditions in the alimentary canal which determine the absorption of water. The question is narrowed by the fact, which has been established beyond doubt by the researches of von Mering, Edkins and others, that the absorption of water in the stomach may be regarded as nil. Although from this viscus alcohol, peptone and sugar may be absorbed to a certain extent, water, or saline fluids introduced into it, are passed through the pylorus either without change, or with their quantities added to by the secretion of fluid from the gastric glands. In no case is there a diminution of fluid in the stomach.

The chief absorption of water occurs in the small intestine. It is on this account that the salient features of cases of dilatation of the stomach with stenosis, absolute or relative, of the pyloric orifice can be nearly all referred to the deprivation of the body of water, and can often be relieved by the administration of water either subcutaneously or by the rectum, *i.e.*, by the channels through which absorption is still possible. The introduction of water into the stomach simply increases the dilatation but does not relieve the intense thirst of the patient. Water that has been swallowed to quench thirst has first to be passed from the stomach into the small intestine before it can be absorbed and relieve the needs of the tissues.

A certain amount of absorption of water, as we have seen, may occur in the large intestine. The intestinal contents at

the ileo-cæcal valve contain relatively nearly as much water as they do at the upper part of the jejunum. Their absolute bulk is however much smaller, so that only a small proportion of the water that has been taken in by the mouth remains to be absorbed in the large gut: an amount probably not equal to that which has been added to the contents of the small intestine in the form of secretion by the stomach, liver, pancreas, and intestinal tubules.

The problem before us is therefore the mechanism of absorption by the intestinal villi. The injection of large quantities of water or normal salt solution into the lumen of the small intestine hardly affects the flow of lymph from the abdominal cavity, any increase in flow being secondary to an increase in the volume of the circulating blood. The passage of fluid from the gut is therefore into the blood vessels. Intervening between the blood vessels and the gut cavity we find only the layer of columnar epithelial cells united together by a certain amount of cement substance. What are the factors concerned in the passage of the fluid across this epithelial layer? The movements of the gut and the movements of the blood provide for practically steady composition on the two sides of the membrane, so that we have to enquire whether the physical differences between the fluid on one side and that on the other of the membrane, taken in connection with the permeability of the cell membrane itself, are sufficient to account for the up-take of water and salts.

If we were dealing with a dead colloidal membrane, such as bladder, parchment paper, or gelatin (permeable both to water and salts), it would be easy to determine the conditions under which the transference of fluid from one side to the other may take place. In such a case the passage of water would depend on the relative molecular concentration on the two sides of the membrane, on the relative diffusibility through

the membrane of the salts on the two sides, as well as on the presence on the one side or other of constituents in solution, or semi-solution, *e.g.*, colloids, to which the membrane was impermeable. Thus, in the case of two solutions A and B separated by such a membrane, if the osmotic pressure, or molecular concentration, of B be higher than A, the force tending to move water from A to B will be equal to this osmotic difference. There is at the same time set up a diffusion of the dissolved substances from B to A and from A to B. The result of this diffusion must be that there is no longer a sudden drop of osmotic pressure from B to A, and the result of the primary osmotic difference on the movement of water

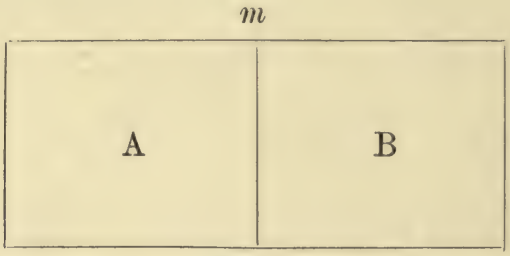


FIG. 2.

will be minimised in proportion to the freedom of diffusion which takes place through the membrane. Now let us take a case in which A and B represent equimolecular and isotonic solutions of α and β. It is evident that the movement of water into A will vary as $Ap - Bp^* = 0$. But diffusion also occurs of α into B and of β into A. Now the amount of substance diffusing from a solution is proportional to the concentration, and therefore to its osmotic pressure, as well as to its diffusion coefficient.

Hence the amount of α diffusing into B will vary as $Ap.\ \alpha k$ (when k is the diffusion coefficient).

In the same way the amount of B diffusing into A will vary as $Bp, \beta k^1$.

* Ap = osmotic pressure of A, etc.

Hence if ak is greater than βk^1, *i.e.*, if a is more diffusible than β, the initial result must be that a greater number of molecules of a will pass into B than of β into A. Hence the solutions on the two sides of the membrane will be no longer equimolecular, but the total number of molecules of $a + \beta$ in B will be greater than the number of molecules of $a + \beta$ in A, and this difference will be most marked in the layers of fluid nearest the membrane. The result therefore of the unequal diffusion of the two substances is to upset the previous equality of osmotic pressures. The layer of fluid on the B side of the membrane will have an osmotic pressure greater than the layer of fluid in immediate contact with the A side of the membrane, and there will thus be a movement of water from A to B. Hence, if we have two equimolecular and isotonic solutions of different substances separated by a membrane permeable to the dissolved substances, there will be an initial movement of fluid towards the side of the less diffusible substance.

We have an exact parallel to this in Graham's familiar experiment in which a porous pot filled with hydrogen is connected by a vertical tube with a vessel containing mercury. In consequence of the more rapid diffusion of the hydrogen outwards than of atmospheric air inwards, the pressure within the pot sinks below that of the surrounding atmosphere, and the mercury rises several inches in the tube. We must therefore conclude that, even when the two solutions on either side of the membrane are isotonic, there may be a movement of fluid from one side to the other with a performance of work in the process.

Indeed, as was shown by Lazarus-Barlow,* osmosis may occur from a fluid having a higher final osmotic pressure

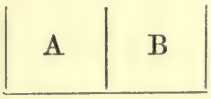
* Lazarus-Barlow. *Journ. of Physiol.*, XIX., p. 140. 1895.

towards a fluid having a lower final osmotic pressure. If, for example, equimolecular solutions of sodium chloride and glucose be separated by a peritoneal membrane, the osmotic flow will take place from the fluid having the higher final osmotic pressure—viz., the sodium chloride. We might compare with this experiment the results of separating hydrogen at one atmosphere's pressure from oxygen at two atmospheres' pressure by means of a plate of graphite. In this case the initial result will be a still further increase of pressure on the oxygen side of the diaphragm—a movement of gas against pressure taking place in consequence of the greater diffusion velocity of hydrogen.

So far we have only considered the behaviour of solutions when separated by a membrane, the permeability of which to salts is comparable to that of water; so that the passage of salts through the membrane depends merely on the diffusion rates of the salts. There can be no doubt, however, that we might get analogous movements of fluid against total osmotic pressure determined, not by the diffusibility of salts, but by the permeability of the membrane to the salts—a permeability which may depend on a state of solution or attraction existing between membrane and salts. We have a familiar analogue to such a condition of things in the passage of gases through an india-rubber sheet. If two bottles, one containing carbonic acid, the other hydrogen, be separated by a sheet of india-rubber, CO_2 passes into the hydrogen bottle more quickly than hydrogen can pass out into the CO_2 bottle, so that a difference of pressure is created between the two bottles, and the rubber bulges into the CO_2 bottle. We might, in the same way, conceive of a membrane which permitted the passage of dextrose more easily than that of sodium chloride. With such a membrane, experiments conducted in the same way as Dr. Barlow's would lead to the diametrically opposite results. The

importance of the membrane in determining the direction of the osmotic passage of fluid is well illustrated by Raoult's experiments mentioned in the first lecture. When alcohol and ether were separated by an animal membrane, alcohol passed into the ether, whereas if vulcanite were employed for the diaphragm, the osmotic flow was in the reverse direction, and an enormous pressure was set up on the alcohol side of the diaphragm.

The next point to be considered is the passage of a dissolved substance across membranes in consequence of differences in the partial pressure of the substance on the two sides of the membrane. Great stress was laid by Heidenhain and his pupil Orlow on the fact that in the peritoneal cavity, as well as from the intestine, sodium chloride may be taken up from fluids containing a smaller percentage of this substance than does blood-plasma; and they regard this absorption as pointing indubitably to an active intervention of living cells in the process. This argument requires examination. Supposing the two vessels A and B to be separated by a membrane which offers free passage to water, and a difficult passage to salts. Let A contain ·5 per cent. salt solution and



B a solution isotonic with a 1 per cent. NaCl, but containing only ·65 per cent. of this salt, the rest of its osmotic tension being due to *other dissolved substances*. If the membrane were absolutely 'semi-permeable,' water would pass from A to B until the two fluids were isotonic, *i.e.*, until A contained 1 per cent. NaCl (to simplify the argument we may regard volume B as infinitely greater). If however the membrane permitted

passage of salt, the course of events might be as follows:— At first water would pass out of A and salt would diffuse in until the percentage of NaCl in A was equal to that in B. There would not be an equal partial pressure of NaCl on the two sides of the membrane, but the total osmotic pressure of B would still be higher than A. Water would therefore still continue to pass from A to B more rapidly than the other ingredients of B could pass into A. As soon however as more water passed only from A, the percentage of NaCl in A would be raised above that in B. The extent to which this occurs will depend on the impermeability of the membrane. When the NaCl in A reaches a certain concentration, it will pass over into B, and this will go on until equilibrium is established between A and B. Extending this argument to the conditions obtaining in the living body, we may conclude that neither the raising of percentage of a salt in a fluid above that of the same salt in the plasma, nor the passage of a salt from a hypotonic fluid into the blood-plasma, can afford in itself any proof of an *active* intervention of cells in the process.

We have already seen that the effective osmotic pressure of a substance, *i.e.*, its power of attracting water across a membrane, varies inversely as its diffusibility, or as the permeability of the membrane to it. What will be the effect, supposing that on one side of the membrane we place some substance in solution to which the membrane is impermeable?

We will suppose that A and B contain 1 per cent. NaCl, but that B contains in addition some substance x to which the membrane is impermeable. Since the osmotic pressure of B is higher by the partial pressure of x than that of A, fluid will pass from A to B by osmosis. But the consequence of this passage of water will be to concentrate the NaCl in A, so

that the partial pressure of this salt in A is greater than in B. NaCl will therefore diffuse from A to B with the result that the former difference of total osmotic pressure will be re-established. Hence there will be a continual passage of both water and salt from A to B, until B has absorbed the whole of A. This result will be only delayed if the osmotic pressure of A is at first higher than B, in consequence of a greater concentration of NaCl in A. There may be at first a flow of fluid from B to A, but as soon as the NaCl concentration on the two sides has become the same by diffusion, the power of x to attract water from the other side will make itself felt, and this attraction will be proportional to the osmotic pressure of x.

In the case of the intestinal cell, the substance x may be represented by the colloids of the blood-plasma circulating in the capillaries, which, as I have shown,* have a definite 'osmotic pressure' or attraction for water equivalent to about 30 mm. Hg., and this minimal attraction would in time determine the transference of the whole of the saline fluid from the lumen of the gut to the blood vessels.

The question how far these conditions for physical absorption are fulfilled in the case of the intestine must be determined by actual experiment on the living animal. We know already something about the permeability of the epithelial membrane lining the intestine. Like all other cells of the body, the free surface of the intestinal cells can be regarded as probably lipoid in character and therefore physically permeable only by such substances as are soluble in such a membrane, *e.g.*, by water, by alcohols, urea, and other substances enumerated in my previous lecture.

The permeability of the cement substances between the cells

* *Journ. of Physiol.*, XIX., 312, 1896.

may possibly be assumed as having a wider scope. If the permeability of the intestinal wall can be deduced from this analogy with other cells of the body, such as red corpuscles, we may assume that the main foodstuffs, *e.g.*, sugar, as well as all the salts, can only obtain entrance into the interior of the villus by the inter-epithelial spaces, while through the cells only such substances can be absorbed as are soluble in lipoid media.

Let us see how far these generalisations, which have been the theme of investigation chiefly by Höber,* bear the test of experiment.

When the paths of absorption are studied by the histological examination of the wall of the gut after the administration of various dyes, only such dyes as are soluble in lipoids are found in the cells lining the intestine, where they accumulate in a granular form. Since the dyes not soluble in lipoids, such as indulin, are absorbed into the system from the alimentary canal, and yet cannot be traced through the cells, Höber concludes that they pass by means of the inter-epithelial cement-substance in a highly dilute condition. None of these dye substances can be regarded however as normal foodstuffs, or as arousing in any way the normal functions of the alimentary mucous membrane, and considerable difficulties are met, if we attempt to draw conclusions from these experiments regarding the path normally taken by such constituents of the food as salts, sugar, or amino-acids. Dextrose, for instance, is absorbed with great rapidity by the small intestine, especially in the upper reaches of the gut. Cane-sugar is also absorbed, but more slowly, and undergoes inversion in the process. This difference in absorbability of

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* See a full account of this work in Höber's article in the "Handbuch der Physikalischen Chemie in der Medizin" (Koranyi and Ritter), p. 328.

mono- and di- saccharide might be referred to their varying diffusibilities, were it not that another closely-related di-saccharide, viz., lactose, is not absorbed at all, except in such animals as possess the ferment, *lactase*, in their intestinal wall. In other animals lactose acts as a purgative, and even in man large doses of this sugar has a laxative action, owing to the slowness with which it undergoes inversion in the intestine. It is difficult to account for these differences between the absorbabilities of various sugars, so long as we locate the path of their absorption in the inert dead cement-substance between the epithelial cells.

Similar difficulties meet us when we attempt to account for the behaviour of saline solutions introduced into the cavity of the gut. If the solutions contain sulphates or tartrates, *i.e.*, salts to whose anions the gut-wall is relatively impermeable, the course of events is very much the same as that which would occur if these solutions were separated from blood-plasma by a dead wall of parchment paper. If they are hypertonic, they increase in amount by the attraction of water from the circulating fluids, until their molecular concentration is equal to that of the blood-plasma. If however they remain in the gut for a considerable time, they are finally absorbed, just as they would be from a tube of parchment paper. This final absorption could be ascribed to the colloids of the blood serum. Very different is the fate of solutions of substances such as sodium chloride. These are rapidly absorbed even when they are slightly hypertonic. If the solutions are strong, *i.e.*, 2 to 3 per cent. NaCl, they may at first increase in bulk by the diffusion of water into them. From the moment of their introduction however, salt is passing from them into the blood circulating through the intestinal wall, and as soon as their total osmotic pressure is reduced to a point a little above that of the blood-plasma, both water and salt begin to be

absorbed. It might be possible in an individual case, by juggling with the factors that I have previously discussed, to explain the final absorption even of solutions of sodium chloride. To do this however, we have to ascribe to the membrane clothing the intestine a property to which we have no analogue in any known dead membrane, viz., an *irreciprocal* permeability for NaCl. Although sodium chloride passes with the greatest ease from the lumen of the gut into the blood vessels, considerable resistance is offered to its passage in the reverse direction. The small amounts which actually pass from the blood into the gut, *e.g.*, into an isotonic solution of glucose, may be entirely attributed to a minimal secretion of succus entericus. This irreciprocal permeability is bound up with the life of the cells covering the mucous membrane, and is at once abolished if these cells be damaged by the addition of small amounts of NaF to the fluid introduced into the gut, or by the action of distilled water or of temporary anæmia. Under these circumstances the rapid absorption of solutions of sodium chloride is abolished, and the changes in the volume and concentration of the fluid introduced into a loop of gut are apparently determined entirely by its molecular concentration.

The irreciprocal permeability of the intestinal wall to NaCl is well shown in the following experiment by Waymouth Reid.*

Dog. 18 kilos. Two 40-centimetre loops of ileum in continuity. Duration of experiment, 15 minutes.

—	Upper Loop.	Lower Loop.
Introduced	30 cub. centims. of 5·74 per cent. solution of glucose.	30 cub. centims. of distilled water.

* *Phil. Trans.*, B., CXCII., 211, 1900.

Water.

—	Recovered.	Absorbed.	Absorbed in per cent. of introduced.
	cub. centims.	cub. centims.	per cent.
Glucose loop	28	2	6·67
Water loop ..	18	12	40·00

Sodic Chloride added from Blood.

Glucose loop .. ·016 grm., *i.e.*, ·057 per cent. in fluid in gut at end of experiment

Water loop.. .. ·058 „ ·322 „ „ „ „

Glucose absorbed .. ·420 „ 24·4 „

Hence more than three times as much sodic chloride entered the water than the glucose solution from the blood owing to the injurious effect of the distilled water on the cells.

Moreover we have distinct evidence that the vitality of the cells involves, not merely a passive preservation of an irreciprocal permeability, but also an active transference of water from one side to the other of the membrane. Waymouth Reid has shown that, if the animal's own serum be introduced into a loop of its intestine, it undergoes absorption. This absorption affects the water and salts more than the protein, so that the percentage of the proteins in the fluid remaining in the intestine is increased. In this case the fluid within the gut is identical with the fluid within the blood vessels. There are no differences in concentration, quality of salts, or osmotic pressure of proteins. Nevertheless, water passes through the cells of the gut from their inner to their outer sides, entraining with it the salts of the serum and a certain proportion of the indiffusible proteins. Any digestive changes in the proteins as a preliminary to absorption can be excluded by the facts that, in these experiments, the intestinal loops were washed free of any trypsin that they contained, and that serum itself has a strong antitryptic action which would prevent its being attacked by even a strong solution of trypsin.

The following two experiments bring out clearly the facts discussed in the foregoing paragraph :—

ABSORPTION OF SERUM FROM INTESTINE (W. REID).

Dog. 16 kilos. Two 80-centimetre loops of ileum. Duration of experiment, ½ hour. Mesenteric vessels of one loop clamped for 20 minutes previous to experiment. Great detachment of epithelium.

—	Organic solids.	Salts.
	grms.	grm.
Introduced into each loop 50 cub. centims. of own serum, holding	3·2465	·4735
Recovered: Normal loop, 35 cub. centims. of serum, holding	2·4847	·3188
,, Previously anæmic loop, 48 cub. centims. of serum, holding ..	2·9573	·4507

Absorbed in ½ hour.

Normal loop.			Previously anæmic loop.	
		per cent.		per cent.
Water ..	15·00 cub. centims., *i.e.*	30·00	2 cub. centims., *i.e.*	4·00
Organic solids	·7618 grm. ,,	23·46	·2892 grm. ,,	8·90
Salts	·1547 ,, ,,	32·67	·0228 grm. ,,	4·81

ABSORPTION OF SERUM FROM INTESTINE (W. REID).

Dog. 23·5 kilos. Two 80-centimetre loops of ileum. Duration 1 hour. One loop washed with ·8415 per cent. solution of sodic chloride, holding ·1 per cent. of sodic fluoride, the other with ·9804 per cent. solution of sodic chloride. Lowering of freezing point of each wash = — ·590° C.

—	Organic solids.	Salts.
	grms.	grm.
Introduced into each loop 50 cub. centims. of own serum, holding	3·6050	·4550
Recovered: Normal loop, 20 cub. centims. serum, holding	1·8740	·1720
,, Fluoride-washed loop, 50 cub. centims. serum, holding ..	3·3700	·4700

Absorbed in one hour.

—	Normal loop.	Fluoride-washed loop.
	per cent.	per cent.
Water ..	30·00 cub. centims., *i.e.* 60·00	0·00 cub. centim., *i.e.* 0·00
Organic solids	1·7310 grm. ,, 48·01	·235 grm. ,, 6·52
Salts	·2830 ,, ,, 62·19	·015 ,, (added) ,, 3·30

Hydrostatic Pressures.

Normal loop .. .. .. 7 to 11 millims. of Hg.
Fluoride-washed loop.. .. 9 to 12 ,, ,,

Lowering of Freezing Point.

Introduced serum.	Removed from fluoride loop.	Removed from normal loop.	Serum of dog at end of experiment.
— ·600°C.	— ·630°C.	— ·560°C.	— ·640°C.

The epithelial cells of the intestine must therefore be actively involved in the absorption of fluid, *i.e.*, a certain proportion of the energy set free within them by the oxidation of their food-stuffs must be employed in the pumping of water and salts from one side of the cell to the other. This conclusion is confirmed by certain experiments of Reid * and Cohnheim,† in which two identical solutions of sodium chloride were separated from one another by a membrane consisting of the whole living intestinal wall. In these experiments it was found that there was active transference from the inner to the outer side of the membrane.

We must conclude that, when a fluid is introduced into the intestine, an active transference of water from the lumen into the blood-stream is effected by the intermediation of forces having their origin in the metabolism of the cells themselves.

* E. W. Reid, *Journ. of Physiol.*, XXVI., 436, 1901.
† Cohnheim, *Ztsch. f. Biol.*, XXXVIII., 419, 1899.

This work of absorption may be aided or hindered according to the physical conditions present. If these act against the cells, *e.g.*, if the fluid be hypertonic, the absorption is effected more slowly, while with hypotonic solutions, the physical conditions concur with the vital activity of the cells in bringing about a very rapid transference of fluid from the gut into the blood vessels. Among these physical conditions, we must reckon the nature of the salts present in the solution. If these can pass easily into and through the cells, *e.g.*, ammonium salts, sodium chloride, absorption is carried out rapidly. If, on the other hand, the salts in the intestinal contents are but slightly diffusible or have very little power of penetrating into the cells, the absorption of water by the cells causes an increased concentration of the salts, and therefore an increased osmotic pressure, which offers a resistance to any further absorption; and the process comes to an end, when the absorptive power of the cells is exactly balanced by the increased osmotic pressure, or attraction for water, of the intestinal contents.

We must therefore ascribe absorption of fluids by the intestines to the activity of the cells clothing the villi. The effectiveness of this activity will be influenced by the osmotic pressure and the quality of the solutions involved, just as the results of the contractions of our muscles will differ according to the resistance which the contractions have to overcome.

Very similar problems to those presented by the intestinal epithelium engage our attention when we investigate the exchanges of fluid through the frog's skin. Under normal circumstances the frog can take in water through its integument in the same way as man can absorb through his intestine. If, for instance, a frog be poisoned with curare and be placed in a vessel with a little water, it is noticed at the end of twenty-four hours that the frog has become dropsical. The action of

curare has been to modify the permeability of the capillaries so as to affect the balance between the production and absorption of tissue fluid in the direction of increased transudation. The water lost to the blood in this way is taken up by the frog's skin.

A very accurate series of observations was carried out by Waymouth Reid * on the factors determining the movement of fluid through the skin. He first showed that the skin, like the intestinal mucous membrane, presents a certain amount of irreciprocal permeability, as evidenced by the fact that the diffusion of water into or out of various solutions differs according as the movement is from within outwards, or from without in. He then investigated the behaviour of the skin when it was used as a diaphragm separating two identical solutions of normal sodium chloride. In this case there was distinct passage of fluid from the outer to the inner side of the skin—a transference which could be explained only on the hypothesis that work was done on the fluid by the cells of the skin itself. That the energy of this work was derived from the normal metabolism inseparable from the life of the cells was proved by adding sodium fluoride, or other deleterious substance, to the fluid used in the experiment, when the cell behaved like ordinary dead membrane, the irreciprocal permeability and the active transference of fluid totally disappearing.

We may conclude therefore that the intake of fluid occurs for the greater part in the small intestine. The presence of fluid in the lumen of the gut gives rise to a stream of water from the gut into the circulating blood, brought about by the activity of the cells clothing this viscus, *i.e.*, by the force set free in the normal metabolism of these cells. This active

* E. W. Reid, *Journ. of Physiol.*, XI., 312, 1890.

absorption may be aided or opposed by the ordinary osmotic factors at work, which depend on the concentration of the fluid introduced into the gut and on the nature of the dissolved salts.

Thus if the solutions contain salts, such as sodium chloride or salts of ammonia, which pass easily through the mucous membrane, the absorption of the fluid is rapidly carried out. If, on the other hand, salts, such as sodium sulphate, which pass with extreme difficulty through the cell lining, are present, the osmotic pressure, due to the dissolved salts, continues as a force opposing the absorptive activity of the cells. Water may be absorbed up to a certain point, viz., until the surplus of the molecular concentration of the salt solution over that of the blood-plasma produces an osmotic pressure or attraction for water which exactly counterbalances the absorbing forces of the intestinal epithelium. It is not surprising therefore that many authors have found that the rate of absorption of any saline solution is proportional to the diffusibility of the salts they contain.

When serum is introduced into the gut, the stream of water carries with it both the dissolved salts and the dissolved protein. In the case of the latter however, there is a certain lag, so that the fluid becomes more and more concentrated in protein, until the intestinal contents become almost solid, and absorption ceases until the serum protein can be broken up by the digestive ferments of the gut. Whether there is an active absorption of dissolved substances apart from water cannot yet be regarded as distinctly settled, though the different rates at which the various sugars are dissolved, as well as the irreciprocal permeability of the membrane for sodium chloride, point to the fact that the cells of the intestine, besides their attraction for water, have the power of picking up out of the intestinal contents those substances in solution

which represent the normal foodstuffs of all the cells of the body.

With this selection of substances the adaptive powers of the intestinal epithelium are exhausted. It has, if we may so express it, little or no feeling of the needs of the body as a whole, and the satisfaction of these needs has therefore to be provided for by the co-operation of the central nervous system, including those higher parts of this system which are involved in the production of appetite.

LECTURE IV

THE EXCHANGE OF FLUIDS IN THE BODY—THE PRODUCTION OF LYMPH

Under the term internal media of the body we include three distinct fluids, all of which may be regarded as derived from the original cœlomic fluid. These are :—

(1) The circulating *blood*, contained in a closed system of tubes and everywhere separated from the tissues by a layer of endothelium.

(2) The *lymph*, also contained in a closed system of endothelial tubes connected at one or more points with the blood vascular system.

(3) The *tissue fluid*, filling all the spaces of the body and in immediate contact with the tissue cells.

This last-named is the real internal medium of the body, into which the cells discharge their waste products, and from which they derive their sustenance as well as their necessary oxygen.

In considering the factors which determine the fluid exchanges of the cells, the composition and amount of the tissue fluid are therefore of extreme importance. Moreover we, as medical men, are especially interested in the quantitative relationships of this fluid, since on this depends, under certain pathological conditions, the production of anasarca or dropsy.

Unfortunately an investigation of the tissue fluids is very much more difficult than is the case with the blood or lymph. We may say, as a general rule, that increased tissue fluid will

tend to produce a more abundant lymph outflow from the part, but we cannot predicate any direct proportionality between these two phenomena. Up to the present I know of only two sets of researches dealing with the amount of tissue fluid present under conditions which may be regarded as more or less normal. In Roy's and Lazarus-Barlow's* experiments the specific gravity of the tissues was used as an index to the amount of tissue fluid present; a diminution in specific gravity being regarded as indication of increase of this fluid. Dr. Oliver† has employed another method for arriving at an idea of this quantity, which, in view of the importance of the point on which knowledge is sought, deserves further investigation with a view to its confirmation. Oliver showed that, if the finger were emptied of blood by means of a rubber ring, a drop of blood obtained from its tip, immediately after relaxing the constriction at the base, was more concentrated than that obtained from the finger which had not been previously emptied. He ascribed this difference to the fact that in the process of emptying, not only is the blood driven out of the capillaries, but there is also a squeezing of the tissue fluid out of the intercellular spaces. He regards blood obtained in the normal fashion as blood *plus* tissue fluid. On comparing this blood with that obtained from the emptied finger, he finds a difference which he takes to be a measure of the tissue fluid present in the finger.

The tissue spaces are separated from both blood vessels and lymphatics by means of endothelium. The situation of the valves in the lymphatic trunks determines that any flow of fluid in these trunks must be from periphery towards centre, *i.e.*, towards the great veins at the root of the neck. The

* W. S. Lazarus-Barlow, "The Pathology of the Oedema which accompanies Passive Congestion." *Phil. Trans.*, p. 779, B, 1894.

† *Proc. Roy. Soc.*, June 11, 1903.

lymphatic radicles form a closed system, so that fluid only slowly escapes from the tissue spaces into them. Thus coloured fluid injected into the tissues passes with extreme slowness into the lymphatics, unless the seat of injection be kneaded. Any movement causing stretching of aponeuroses or skin, by increasing the pressure in the subjacent tissues, will empty the tissue spaces into the lymphatics. The fluid lost in this way must be replenished at the expense of the blood. This is continually being renewed in every part of the body, and therefore bringing up new fluid to the tissues to replace that lost by way of the lymphatics.

Most of our opinions as to the factors which determine the production of tissue fluid are derived from the study, not of the fluid itself, but of the lymph flow from the tissue. It is evident that considerable reserve must be exercised in drawing conclusions as to the amount and composition of the fluid passing from the blood vessels into the tissue spaces, from experiments carried out on the composition and amount of the lymph flowing away in the lymph channels. More especially is this the case since, as we shall see, fluid as well as substances in solution may be taken away from the tissues, not only by the lymphatics, but also by the blood vessels themselves. Hence the fluid obtained from a cannula in the lymphatic trunks represents only that portion of the transuded fluid which has escaped reabsorption by the blood vessels. Its composition will approach that of the transuded fluid more nearly the greater the rate at which this is produced, but in every case will be modified in consequence of the metabolic exchanges occurring between the fluid and the cells it bathes.

If however we bear these limitations in mind, we may, by study of the lymph-flow from a part of the body, arrive at some approximate idea of the factors involved in the

production of tissue fluid from the blood vessels. Here, as in all similar investigations, we have to measure accurately the physical forces concerned and the energies which are available for the production of the fluid, before we can come to a conclusion as to the part played by the cells of the blood vessels and tissues in the process. What are these factors? The production of tissue fluid is limited to the region of the capillaries and small veins. Through these blood is flowing at a pressure varying in different localities and according to the position of the body. With the body in a horizontal position the average capillary pressure may be taken as something between 20 and 30 mm. Hg. In the upright position this figure may be considerably increased by the addition of the hydrostatic pressure due to the column of blood between the heart and the lower portions of the body. In the capillaries of the liver the pressure will be lower, probably about 10 mm. Hg.

The endothelial wall of the capillaries presents a structure which would suggest the possibility of a leakage or filtration. The separate flat cells of which it is composed abut on the adjacent cells, but are not directly continuous with these, a slender crack being left containing either lymph or cement substance, probably the former, which stains black with nitrate of silver. The cells themselves are not indefinitely extensible, so that distension of the vessels causes a widening of the intercellular cracks as shown by the coarse lines presented by a silver-stained specimen.

It is very difficult to determine whether the cells themselves permit the passage of the fluid constituents of the blood, as we have seen to be the case in the intestine; but that the cracks between the cells will allow of the passage of fluid is suggested by the fact that under abnormal conditions white and red corpuscles may pass out by these channels. Assuming

that the vessel wall is passive in the production of tissue fluid, we should have to regard it as a more or less perfect colloidal membrane, and the conditions of transudation would be given to us by a study of the behaviour of colloidal membranes of various degrees of density, or permeability. A comparative study of such membranes has been recently made by Bechhold.* It was shown many years ago by Graham that colloidal membranes were impermeable for dissolved colloids. Bechhold shows that this impermeability is relative. Thus, a membrane impregnated with 3 per cent. gelatin might allow hæmoglobin to pass through but would keep back serum albumin and serum globulin; on increasing the concentration to 4 per cent. hæmoglobin might be retained but albumoses and dextrines would still pass.

This impermeability of colloid membranes may be used, as was shown by Martin,† to separate the saline and fluid constituents from colloid solutions such as serum. For this purpose a gelatin membrane is deposited in the meshes of a Chamberland filter, and in order to obtain an appreciable amount of filtrate in a given time very high pressures are used, *i.e.*, 30 to 40 atmospheres. Such high pressures are however only necessitated by the great resistance offered to the passage of fluid through these thick membranes. When a thin membrane is employed, such as a film of gelatin deposited on a piece of peritoneum, a separation of water and salts from the serum appears at a pressure below 40 mm. Hg. As we have already seen, there is a limiting pressure below which no filtration takes place, any filtrate being reabsorbed by the colloid solution. This limiting pressure, which in serum amounts to about 30 mm. Hg., I regard as equivalent to the osmotic pressure or '*Quellungsdruck*' of the proteins of the

* *Zeitsch. f. physikal Chem.*, LX., p. 257, 1907.

† *Journ. of Physiol.*, XX., 364, 1896.

serum, or rather of those constituents of the serum to which the gelatin membrane is impermeable.

If therefore the capillary wall were equivalent to a membrane of 10 per cent. gelatin, it would allow the passage of a protein-free transudate containing all the water and salts of the blood-plasma, so long as the pressure of the capillaries exceeded 30 mm. Hg.; whereas if the pressure fell below this figure, any protein-free transudate present in the tissue spaces would be reabsorbed into the blood vessels. If the membrane, like a 2 per cent. gelatin solution, were partially permeable to proteins, the effect would be to lower the difference of pressure necessary to give transudation, *i.e.*, we might have transudation at a pressure of 10 to 20 mm. Hg. The transudate would then contain protein, and the percentage of protein in the transudate would approach nearer and nearer to that of the circulating plasma the more permeable were the vessel-wall.

Pressure differences would not be the only factor determining the transference of water and dissolved substances through the capillary wall. We have reason to believe that the capillary wall is permeable to, *i.e.*, allows of the diffusion of practically all crystalloids, though the ease with which the various salts will pass differs according to the nature of the salt. Sodium chloride, for instance, escapes through or between the endothelial cells with greater rapidity than sodium sulphate. The capillary wall resembles in this respect the epithelial lining of the intestine.

Any sudden formation of soluble substances outside the vessels will tend, by raising the molecular concentration of the tissue fluid, to draw water from the blood, and therefore to add to the state of distension of the tissue spaces. On the other hand, an increased molecular concentration of the blood, such as may be produced by the injection of concentrated

solutions of dextrose or sodium sulphate into the circulation, will draw water from the tissue spaces, and these in turn will draw water from the cells of the tissues. The effect however will not be permanent, since the dissolved substance present in excess, either outside or inside the vessels, will gradually diffuse through the vessel-wall so that the molecular concentration on both sides will be equalised. The greater the resistance offered by the vessel-wall to the diffusion of the salt, or crystalloid, the greater will be the effect as judged by transference of fluid. Sodium sulphate, for instance, which passes with difficulty through the capillary wall, will cause a greater degree of hydræmic plethora than an equivalent solution of sodium chloride.

In investigating the factors concerned in the production of tissue fluid and lymph, our first care must be to see how far the pressure differences existing between the blood and the tissue spaces are responsible for the passage of fluid into these spaces. We must then enquire into the part played by the differences of concentration, and finally see whether any effects remain, which are inexplicable as results of hydrostatic pressure or osmotic differences and must therefore be referred to an active intervention on the part of the endothelial cells themselves.

(1) *The Part Played by Pressure Differences.*—Much confusion has crept into the interpretation of the experiments on lymph formation by neglecting to give due importance to the great differences which exist between the conditions of lymph formation in various parts of the body. According to Ludwig's filtration hypothesis, the amount of tissue fluid formed in any part should be proportional to the difference between the intracapillary blood pressure and the pressure ruling in the extracapillary spaces. Where there is normally a considerable production of tissue fluid and an easy access for this fluid

into the lymphatics we should expect to find, if the hypothesis be correct, that the lymph flow also varies with this difference of pressures. This condition is found in the abdominal organs. The fact that all the lymphatics of the body, with the exception of those on the upper part of the chest, finally pour their contents into the thoracic duct, has led many to doubt the possibility of drawing conclusions as to lymph production by observations carried out on the lymph flow through this duct. It is easy to assure oneself that this objection is without weight, since under normal circumstances the lymph flow from practically all parts of the body, except the abdominal viscera, is so small that the part it contributes to the thoracic duct lymph may be neglected.

By a process of exclusion we can show that the only organs which contribute an appreciable quantity of lymph to the thoracic duct are—

(a) the alimentary canal;

(b) the liver;

the thoracic organs, the limbs, and the kidneys being practically negligible so long as active movements are not being carried out. It is not possible to exclude the intestinal lymph from the thoracic duct, but it is quite easy, by ligaturing the lymphatics in the portal fissure, to shut off the lymph produced in the liver, and so to obtain only that flowing from the alimentary canal.

In both these organs we can alter the pressure difference between the blood and tissue spaces by altering the pressure in the blood capillaries. It is found that every procedure which raises the pressure in these capillaries increases also the lymph flow from the part affected.

The lymph flow from the thoracic duct varies considerably from animal to animal, and may amount in ten minutes to anything between 1 cc. and 10 cc. Ligature of the liver lymphatics

causes as a rule a diminution of the flow, perhaps by one-half, the solid constituents of the lymph being at the same time diminished. If the portal vein be ligatured, a very large rise of pressure is immediately produced in the capillaries of the intestinal area, and this rise of pressure is associated with a considerable increase in the amount of lymph flowing from the duct. On obstructing the inferior vena cava above the diaphragm there is a great rise of pressure in the vessels of the liver, but with a coincident fall of arterial pressure: the intestines become blanched while the liver swells. This rise of pressure in the hepatic capillaries is associated with a large increase in the lymph flow from the thoracic duct, an increase which is absent if the liver lymphatics have been previously ligatured.

The area of increased lymph production is therefore limited to the area where the intracapillary pressure is raised. The different sources of the lymph obtained in these experiments is also shown by the difference in its composition, the lymph derived from the liver being more concentrated than that derived from the intestines. Liver-lymph in fact contains nearly as much protein as does the circulating blood-plasma. These experiments show that there are marked differences between the intestine and the liver in the mechanical resistance to filtration of the fluid constituents of the plasma. Normally the pressure in the intestinal capillaries may be taken as between 20 and 30 mm. Hg.; in the liver capillaries between 5 and 10 mm. Hg. On ligature of the portal vein, the pressure in the intestinal capillaries probably rises to between 60 and 80 mm. On obstruction of the hepatic veins, the pressure in the capillaries of the liver rises to about 40 mm. Hg., and the pressure in the intestinal vessels cannot be below this level. Yet the lymph-flow from these two organs during rest can be regarded as approximately

equal, though the pressures are so different; and the lymph-flow from the liver under a pressure of 30 to 40 mm. Hg. may be two or three times as large as the lymph-flow from the intestines with a capillary blood pressure between 70 and 80 mm. Hg.

That the greater ease with which fluid escapes from the blood in the liver is connected with the permeability of the filtering membrane is shown by the difference in the protein concentration of the two sets of lymph. A coarse meshed filter allows not only easy filtration but the passage of all the protein constituents of the filtering fluid, while a fine meshed filter keeps back a certain percentage of the proteins and requires a higher pressure in order that filtration should take place at all.

Again, if the descending thoracic aorta be obstructed, the pressure in the intestinal capillaries must fall to between 10 to 20 mm. Hg., and the same pressure will be found in the hepatic capillaries, *i.e.*, there is a great fall in the normal pressure of the intestinal capillaries, but no appreciable fall in the hepatic capillary pressure. The lymph flow from the thoracic duct under these circumstances is generally diminished, but not abolished, and the lymph at the same time becomes more concentrated. If however the liver lymphatics be previously ligatured, obstruction of the thoracic aorta entirely stops the flow from the thoracic duct, showing that previously the whole of the lymph had been derived from the liver, viz., from the region where the intracapillary pressure was not appreciably altered. The wall of each capillary seems to be constructed to resist a certain pressure. Variations in this pressure will affect the amount of transudation without reference to what may happen to be the absolute height of the pressure attained.

When we come to deal with the production of tissue fluid in

the limbs and subcutaneous tissues, the enquiry becomes more complex and the results more difficult to interpret, owing to the fact that in the resting limb there is no flow from the tissue spaces at all. This absence of flow may be ascribed either to relative impermeability of the capillary wall itself, or to an increased resistance presented to the passage of fluid from the tissue spaces into the lymphatic capillaries. That some part, at any rate, is played by the latter factor is indicated by the fact that if a coloured fluid, such as solution of Berlin blue, be injected under the skin, it finds its way into the lymphatics with extreme slowness, unless its absorption is facilitated by kneading the limb or by carrying out passive movements. Ludwig has shown that the lymphatics of the aponeuroses are so arranged that every movement, active or passive, tends to pump fluid from the tissue spaces into the lymphatics, and from the smaller into the larger lymph trunks. Experiments on the production of lymph in the limbs have therefore always to be associated with kneading or passive movements in order to get any flow of lymph at all. Experimenting in this way, we find that alterations of the pressure in the capillaries of the limb effect changes in the lymph flow which are insignificant as compared with those observed under similar conditions in the abdominal organs. Obstruction of a large venous trunk has, in most experiments, been attended with a trifling increase of lymph production, but arterial hyperæmia has often had little or no effect, and many authorities, among them Heidenhain, have concluded that there is no appreciable connection between the intracapillary pressure and the production of tissue fluid.

The results however may be very different if, instead of measuring the lymphatic outflow from the limb, we determine the amount of tissue lymph contained in its meshes by one of

the methods which I mentioned earlier in this lecture. Thus although Lazarus Barlow was unable to detect any noticeable difference in the specific gravity of muscle as a result of moderate venous congestion,* he found that any relative increase in the circulation of blood through a limb (as would be caused by the application of Esmarch bandages to the other limbs) caused a fall in the specific gravity of the muscle and a rise in the specific gravity of the blood. † These changes he interpreted as indicating an increased transudation of tissue fluid.

According to Oliver a similar parallelism is found between the amount of tissue lymph in the finger and the general blood pressure. I reproduce here some curves (Figs. 3 and 4, p. 74) in which this connection between the amount of tissue lymph and blood pressure in man is graphically represented. We may conclude that whereas in the limb the turgescence of the tissues, *i.e.*, the distension of their spaces, is probably closely connected with the intracapillary pressure, the increase of tissue fluid produced by a rise of pressure does not normally attain such an extent as to cause an overflow into the lymphatics and therefore a marked parallelism between the lymph flow and the capillary blood pressure. We shall have occasion to return to this point later on when dealing with the factors which determine the production of dropsy.

We may here note simply that it is possible, by altering the nutritional conditions of the tissues, to bring about a condition of affairs in the limb very closely analogous to that found to exist in the abdominal organs. If a limb be scalded so as to induce a state of inflammation, the lymph flow from the limb is largely increased, the lymph becomes richer in proteins, and its amount varies regularly and in proportion to the capillary blood pressure.

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* *Phil. Trans.*, B, 1894, p. 779.
† *Journ. of Physiol.*, Proceedings, Vol. XVI., 13, 1894.

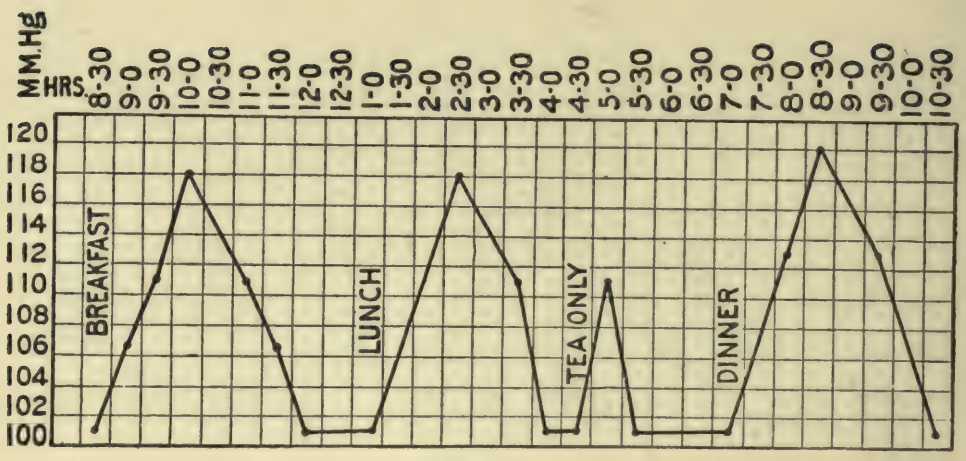

FIG. 3.

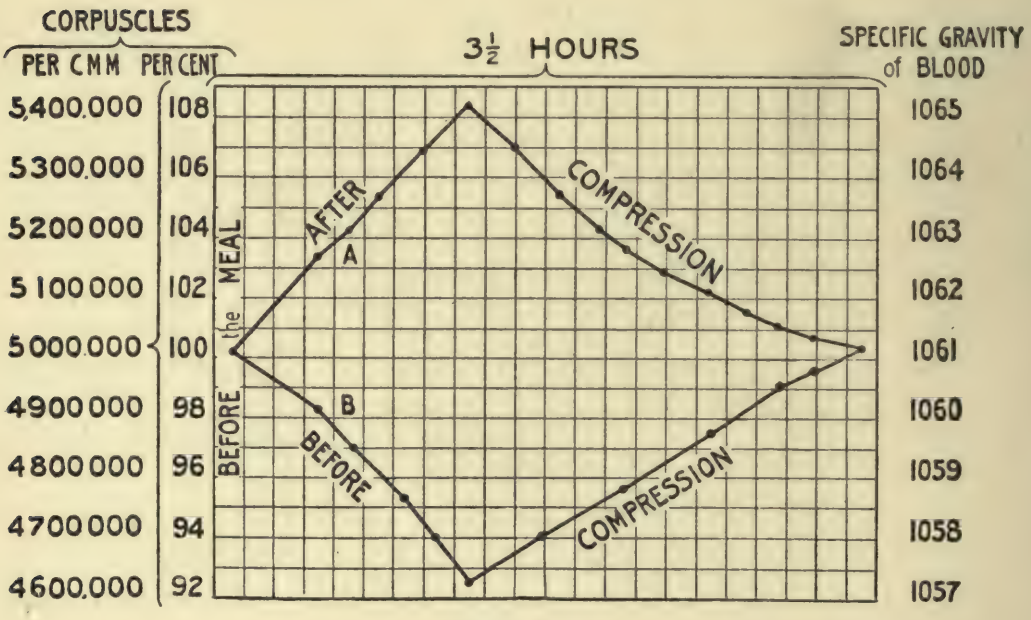

FIG. 4.

FIG. 3. Blood pressure in man, taken by Oliver's method in the radial artery, to show variations in blood pressure induced by the ingestion of food.

FIG. 4. Percentage of corpuscles (5,000,000 per cb. mm. = 100) in blood from finger at different times after taking a meal. The difference between the two curves gives a measure, according to Oliver, of the amount of tissue lymph present in the tissue spaces of the finger (Oliver).

The close connection between capillary blood pressure and transudation of fluid into the tissue spaces is shown when we alter the total amount of the circulating blood. An increase in volume of the circulating blood is accommodated by a dilatation of the arterioles, especially in the splanchnic area, and by a dilatation of the veins. The arterial pressure is unaltered or slightly increased; but there is a considerable relative rise of pressure in the veins near the heart as well as in the portal vein. The velocity of blood flow through the dilated vessels may be increased two- or three-fold so that there is a rise of pressure in all the capillaries of the body. The effect of this rise on lymph production is best marked in the abdominal organs. In the limbs we shall have increased turgescence, *i.e.*, filling of the tissue spaces, but no great increase in the lymph flow. From the liver and intestines the lymph flow may be very largely increased, and this increase results in a concentration of the blood as well as of the plasma, since it involves the escape of a fluid from the vessels which is less concentrated than the circulating plasma. The same effect is seen if we produce a *relative* plethora, not by injection of defibrinated blood, but by causing universal constriction of the blood vessels, as, *e.g.*, by injection of adrenalin. It is sufficient to raise the blood pressure by 50 mm. Hg. for the period of a few minutes to increase the concentration of the blood by 10 or 15 per cent.

These experiments show us not only that the production of tissue lymph is dependent on the difference between the pressures inside and outside the vessels, but also that the permeability of the vessel-walls themselves exercises an important influence on the process, so that filtration as a factor in lymph production is best marked in those parts of the body, such as the liver, where the resistance of the wall of the blood vessels is only just sufficient to keep back the formed elements of the blood.

The formation of tissue fluid will be affected also by chemical conditions, *i.e.*, by the chemical character of the circulating fluid or of the fluid in the surrounding tissue spaces. Let us examine first the influence of changes in the composition of the blood. The chief resistance to the escape of plasma through the cracks between the endothelial cells is afforded by the presence of proteins dissolved in this fluid. The less the protein contained in the plasma, the more easily will it filter through any membrane, and the more easily will a filtrate free from protein be separated from it by filtration through a colloid membrane.

It is not surprising therefore to find that a reduction of the protein content of the plasma is associated with an increased production of lymph, and with a greater susceptibility of the lymph production to changes in capillary pressure. If hydræmic plethora be induced by large injections of salt solution into the blood vessels, a very rapid lymph flow, as much as 10 to 20 cc. per minute, may be observed from the thoracic duct. In the production of this fluid however, the co-operation of two factors is involved, viz., altered composition of the blood, and a rise of capillary pressure in all the abdominal viscera. The latter can be avoided by drawing off from the animal an amount of blood equal to that of the normal saline fluid injected. When a pure hydræmia is produced in this way, the lymph flow is increased, but only to an amount about twice as great as that obtained from the same animal before the hydræmia was produced.

Closely connected with the increased lymph-flow obtained in conditions of hydræmic plethora is that observed after the injection of a strong solution of crystalloids, such as sugar, sodium chloride, or sodium sulphate, bodies which were included by Heidenhain in his second class of lymphagogues.

If, for example, 30 cc. of a 30 per cent. solution of dextrose be injected into the jugular vein of an animal, the immediate

effect is to raise the molecular concentration of the circulating blood, and therefore its osmotic pressure. The capillary wall, like all other animal membranes, permits of the passage of water with the greatest ease. Water therefore passes from the tissue spaces into the blood, and the molecular concentration rises in the tissue spaces. This in its turn induces a passage of water from the tissue cells into the spaces. The final result is increased molecular concentration of all the constituents of the body and a change in the spatial distribution of the water, the cells being shrunken and the tissue and blood fluids increased. As a result of the increased volume of circulating blood, a condition is produced analogous to that which can be brought about by the injection of normal salt solution into the circulation, viz., an hydræmic plethora.

As in this latter condition the increased bulk of circulating fluid causes an alteration in its distribution, the normal arterial pressure can only be maintained by opening what Foster calls the "splanchnic flood gates" and thus allowing the surplus blood to distend the capillaries and big veins in the abdomen and in the neighbourhood of the heart.

A study of the pressures in the different parts of the vascular system shows that the results are the same whether the hydræmic plethora be induced by the injection of large quantities of normal salt solution, or by the injection of small quantities of concentrated salt solution. In the latter case however, increased fluid is derived from the cells, and a plethysmograph record shows that all parts of the body, except the abdominal organs themselves, shrink. If we place a limb and an abdominal organ—whether kidney, intestine or liver—into plethysmographs, we find that injection of hypertonic solution causes an almost instantaneous shrinking of the limb associated with an increased volume of the abdominal organ.

As in hydræmic plethora these changes in blood pressure and blood constituents cause a very largely increased production of lymph in the abdominal organs, and a great increase in the lymph flow from the thoracic duct. That the mechanical changes induced by injection of strong salt solution are mainly responsible for the increased lymph-flow is shown by the fact that, if we prevent them by the withdrawal of the appropriate quantities of blood, there is practically no increase of lymph. These facts are well shown in the accompanying curves (Figs. 5 and 6), which represent graphically the results of the typical experiments, of which the chief data may be here quoted.

A. Effect of Injection of Crystalloids on the Blood Pressure.

Bitch. 8 kilos.

Time.	Fem. art.	Portal vein.	Inf. cava.
11.15 ..	100 mm. Hg.	80 mm. $MgSO_4$	12 mm. $MgSO_4$
11.16 to 11.20	40 grms. dextrose in water (50 cc. fluid) injected		
11.20 ..	65 ..	210 ..	180
11.30 ..	105 ..	147 ..	50
11.40 ..	120 ..	120 ..	25
11.50 ..	118 ..	120 ..	17
12.0 ..	114 ..	124 ..	18
12.15 ..	107 ..	126 ..	18

Effect of Injection of Crystalloids on Lymph-flow.

Dog. 12 kilos. Kidney vessels ligatured.

Lymph in 10 mins.
3 cc.
3·6
30 grms. dextrose in 30 cc. water injected into jugular vein.
33
31
20
12
9
8·4
6·4

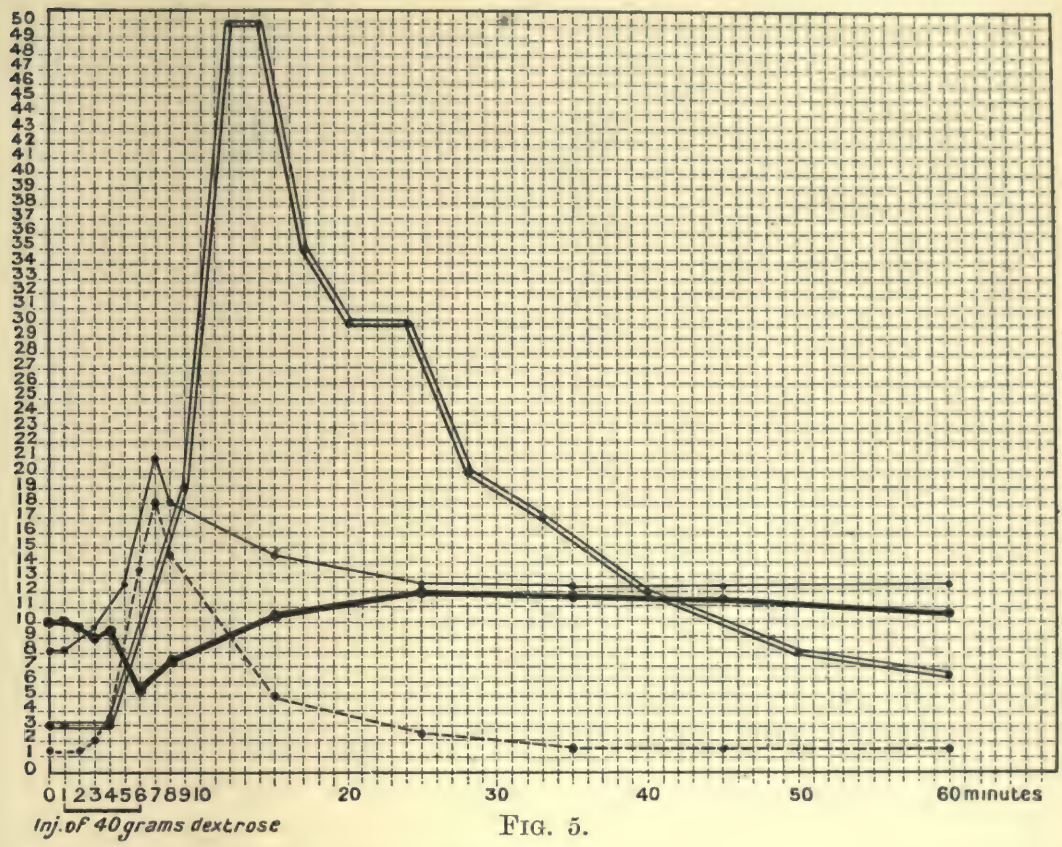

FIG. 5.

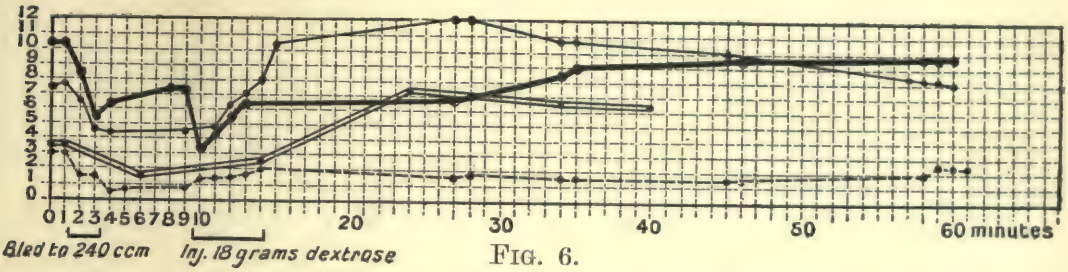

FIG. 6.

FIGS. 5 AND 6.—Curves showing the relation between the pressures in the portal vein, inferior vena cava and carotid artery and the lymph flow from the thoracic duct, after injection of a strong solution of dextrose. In Fig. 6 the rise of pressure was prevented by bleeding.

In both curves the divisions of the abscissa indicate minutes.
Each division of the ordinates expresses:
(*a*) Rate of flow of lymph (in c.cm. in 10 minutes).
(*b*) Height of pressure in femoral artery (in cm. Hg).
(*c*) Height of pressure in portal vein and vena cava (in centimetres $MgSO_4$ solution).
Each curve represents two experiments, one in which the three pressures were recorded, and a similar one in which the lymph-flow and the arterial pressure were recorded. In each case experiments were chosen in which the arterial pressures underwent corresponding changes.
The double line = rate of lymph-flow.
The thick line = pressure in femoral artery.
The thin line = pressure in portal vein.
The dotted line = pressure in inferior vena cava.

B. Effect of Injection of Crystalloids, after previous Bleeding, on Blood Pressures and Lymph Flow.

Time.	Fem. art.	Portal vein.	Inf. cava.
11.45 ..	101 mm. Hg.	78 mm. $MgSO_4$	30 mm. $MgSO_4$
Dog bled to 240 cc.			
11.50 ..	61 ..	45 ..	8
11.55 ..	72 ..	46 ..	9
18 grms. dextrose injected.			

Time.	Fem. art.	Portal vein.	Inf. cava.
12.15 ..	70 mm. Hg.	120 mm. $MgSO_4$	18 mm. $MgSO_4$
12.20 ..	90 ..	108 ..	17
12.30 ..	98 ..	97 ..	14
12.45 ..	98 ..	82 ..	22

Dog. $10\frac{1}{2}$ kilos.

Lymph in 10 mins.

4·6 cc.
3·2 cc. Bled to 350 cc.
1·5
25 grms. dextrose in 25 cc. water injected.
3·5
7·2
6·8.

A study of the comparative amounts of the injected crystalloid in blood and lymph respectively led Heidenhain to the conclusion that there was an actual secretion of lymph from the blood vessels, since, at any given time after the injection, the lymph contains a larger percentage of the injected crystalloid than is to be found in the blood. As Cohnstein pointed out, this difference is due merely to the fact that the amount of sugar is continually declining in the blood, so that the lymph obtained from the thoracic duct at any moment represents the fluid which has transuded from the blood vessels at some unknown time previously, when the sugar content of the blood was at a higher level. At no time is the proportion of the injected crystalloid in the lymph found to be higher than or even to attain to the maximum which is produced in the blood as the result of the injection.

From these various observations we may conclude that the driving force for the production of lymph, or tissue fluid, is represented by the difference between the pressure in the capillaries and the pressure in the tissue spaces outside the capillaries. The amount actually formed in any organ of the body under a given pressure is conditioned by the permeability of the capillary wall, and perhaps by the ease with which the fluid escapes from the extracapillary spaces into the lymphatics.

We have seen no reason to ascribe any part of the process to the active intervention of, *i.e.*, the evolution of energy by, the cells of the capillary wall, or by the cells of the tissues outside the capillaries. Yet many physiologists are still of opinion that we are not justified in thus excluding cell activity as an agent in the production of lymph. Let us examine some of the arguments which have been put forward against the views which I have represented. I would point out at the outset that we are not justified in assuming an unknown cause so long as phenomena can be explained by a cause which is familiar to us. Nor are we justified in rushing to the explanation of 'vital activity' as soon as phenomena present themselves which are apparently irregular in their incidence and present difficulties in their causation. The one common feature of all cell activity is *adaptation*, and we must show that any assumed activity of the cells, besides involving expenditure of energy by the cells, is also orderly and adapted. To call in vital activity as a sort of irresponsible deity to explain irregularities in our experimental results is an unscientific and I might say cowardly device.

When we examine the lymph flow from any part, we find as a rule that there are minute differences in the proportion of salts that it contains as compared with the blood-plasma,

and that its total molecular concentration is somewhat higher than that of the blood.* This is, after all, what one would expect. The lymph bathes the tissue-cells on its passage into the lymphatics; from these cells it receives the diffusible metabolites resulting from their activity. Many of these will pass by diffusion into the surrounding blood vessels. A certain proportion, including the less diffusible, will be carried away by the lymph stream and will raise the molecular concentration of this fluid.

This rise in molecular concentration, which results in a living cell or tissue as a result of normal activity, can be easily shown in the case of muscle. When pronounced it must act as an additional driving force for the lymph, since any increase in the molecular concentration of the extra-vascular fluid will cause an osmotic flow of water from the vessels into the surrounding spaces. By such a mechanism we may account for a small increase in lymph production, which, according to Asher and Bainbridge, accompanies activity in the submaxillary gland, as well as for the more definite increase in the lymph flow from the liver when the activity of this organ is excited by the injection of bile salts into the circulation.

There is no need to assume in this case that the tissue cells exercise some sort of mystical attraction on the fluid constituents of the blood-plasma. It is conceivable, though not proved, that certain metabolites might cause more or less contraction of the endothelial cells, so increasing their permeability, but there is no evidence for the existence of such a mechanism, and still less for the assumption that energy

* Carlson finds that the lymph flowing from the cervical lymphatic or from the salivary glands may have a molecular concentration considerably below that of the blood plasma. His results are however so irregular, that it is difficult to draw any conclusions as to their significance.

for the passage of the fluid from the blood vessels to the tissue spaces is furnished by the metabolic activity of the endothelial cells, *i.e.*, that these cells act as little machines or motors for the production of lymph.

I must say I am unable to appreciate the stress which has been laid by some authors on the fact that the flow of lymph from the thoracic duct may continue for some time after death. Surely the fact that lymph continues to be produced in a dead animal can hardly be regarded as an argument for the vital intervention of cells in the process. This *post mortem* flow of lymph is best marked in cases where during life the lymph production has been largely increased as the result of the injection of some form of lymphagogue. When the animal dies by stoppage of the heart, the big veins and liver capillaries are full of blood at a pressure which may be greater than the normal; the liver-cells may contain fluid vacuoles and the lymphatics both of the liver and intestines are distended with lymph. All the tissue spaces of the abdomen are in a condition of turgescence. It is not surprising that after death the turgescence gradually diminishes, the shrinking of the distended spaces causing a gradual expulsion of the lymph into the cisterna magna and along the thoracic duct, while the flow, due to the simple emptying out of the preformed lymph, may, so long as the pressure in the liver capillaries remains positive, be aided by the continuance of the process of transudation, *i.e.*, by a new formation of lymph from the liver capillaries.

Among the lymphagogues described by Heidenhain are a series of bodies which he places in a class by themselves, all of which are active poisons and include such substances as commercial peptone, leech extract, extract of crayfish, etc. The action of these bodies, as I showed in 1894, is practically confined to the liver. This is seen in the records of two

experiments, in one of which the portal lymphatics were ligatured. Their injection evokes an increased flow of lymph from the thoracic duct, which is more concentrated than the mixed lymph obtained before the injection (Fig. 7). Their action has been variously interpreted as due to stimulation of

EFFECT OF INJECTION OF DECOCTION OF MUSSELS ON THORACIC DUCT LYMPH.

A. Portal lymphatics free.

Lymph in 10 mins.	Total solids in lymph.
3·6 cc.	—
3·6 cc.	4·93 per cent.
A decoction of mussels injected into jugular vein.	
26 cc.	5·94 per cent.
23 cc.	5·89 ,,
21 cc.	—
19·6 cc.	—
16 cc.	—
13 cc.	5·38 per cent.

B. Portal lymphatics ligatured.

Lymph in 10 mins.	
2·8 cc.	—
3·2 cc.	3·53 per cent.
A decoction of mussels injected into jugular vein.	
3 cc.	3·88 per cent.
4 cc.	—
3·2 cc	—
2·8 cc.	3·73 per cent.

the capillary endothelium (Heidenhain), or to stimulation of the secreting cells of the liver (Asher). For neither of these views is there any sufficient evidence. The lymphagogues do not produce an increased flow of bile, nor does the lymph obtained as a result of their injection differ from the transudation produced under other circumstances in the liver. Heidenhain based his view of their stimulating action on the endothelial cells on the fact that prolonged ischæmia of the

liver, brought about by obstruction of the thoracic aorta, rendered any subsequent injection of these lymphagogues

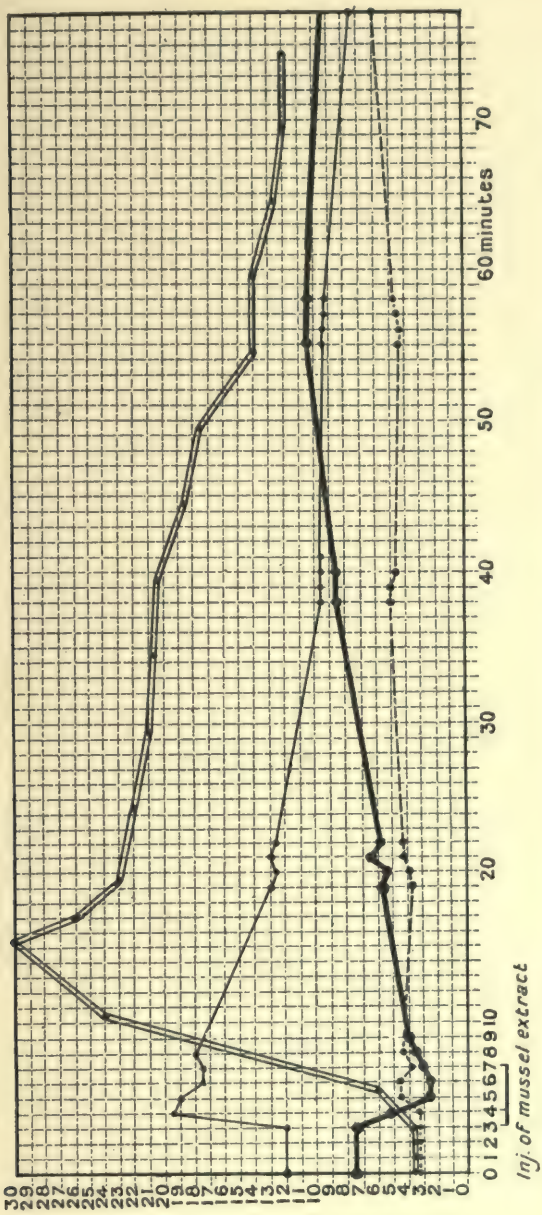

FIG. 7.—Curves to show effect of injection of a lymphagogue of the first class (Heidenhain) on the lymph flow and the blood pressure It will be seen that, although a rise of pressure is produced in the portal vein, the increased lymph flow persists long after all the pressures have returned to normal.

without effect. If we repeat this experiment of obstruction of the thoracic aorta, we find that, on admitting blood at the end of an hour's obstruction, there is a rapid rise of pressure

in the portal vein, pointing to a considerable obstruction in the liver capillaries. During the first twenty or thirty minutes after the blood has been let in, the lymph flow from the thoracic duct is largely increased and contains blood corpuscles, pointing to severe injury of the capillary walls. Details of such an experiment are given here.

EFFECT OF ABDOMINAL ISCHÆMIA ON LYMPH FLOW.

Time.	Lymph in 10 mins.	Lymph.	
11.0—11.10	3·6 cc.	3·6 cc.	Aorta blocked at 11.25.
11.25—1.25	1·6 ,,	17 ,,	Aorta released at 1.25.
1.25—35	6 ,,	6 ,,	(Bloody).
35—45	9 ,,	9 ,,	,,
45—55	9·2 ,,	9·2 ,,	,,

EFFECT OF LONG CONTINUED ISCHÆMIA ON BLOOD PRESSURE IN ABDOMINAL VESSELS.

Dog. 15½ kilos. Consecutive readings at one minute intervals.

Time.	Fem. art.	Portal vein.	Vena cava.
	96	100	30
	96	100	30
12.0 midday	12 (aorta obstructed)	51	36
	8	48	36
	8	51	44
	8	54	44
	8	54	44
1.0 p.m.	9	52	42
2.0 p.m.	9	49	30
	75 (obstruction relieved)	180	26
	74	260	36

It is not surprising that a capillary wall, which has been disorganised in this way by prolonged anæmia, should not betray any further change of its permeability as the result of an injection of a substance which is normally poisonous for it. I agree with Heidenhain that the lymphagogue effect of these substances is due to a direct action on the lining cells of the capillary vessels. But whereas he regards their action

as that of a stimulant to increased activity, I regard them as diminishing the vital properties of the capillary wall, and therefore its resistance to the transudation of fluid.

In a subsequent lecture I hope to show that the balance of forces, which determine the distribution of the fluid of the body, can be accounted for on the so-called mechanical theory of lymph formation which I have set forth above, and that we get no aid in our explanation of the manifold adaptations of the vascular system from the assumption of an active co-operation of the endothelial or tissue cells in the production of lymph.

LECTURE V

THE ABSORPTION OF THE INTERSTITIAL FLUIDS

Any diminution of the total fluid of the body must involve, as a first step, the taking up of the interstitial fluid into the circulating blood, in order that it may be carried to the organs, such as kidneys, lungs or skin, by which it is excreted.

The mechanism of this absorption cannot be regarded at present as settled. In my last lecture I had occasion to speak of the absorption by way of the lymphatics, and there mentioned the anatomical mechanisms described by Ludwig, Recklinghausen, and their pupils, by means of which all the muscular movements of the body, including those of respiration, were utilised for the pumping of fluid from the tissue and serous spaces into the lymphatics, and along these into the blood stream. This mode of absorption from most parts of the body must require considerable time. It is the only way which is open to insoluble particles, such as Indian ink used in tattooing or micro-organisms, living or dead, which have effected an entrance into the tissues.

The question arises as to how far the lymphatic channels are necessary for the absorption of the normal constituents of lymph. Pathological evidence certainly appears to indicate that for certain of the normal constituents lymphatic channels are necessary. We know that complete obstruction of these lymphatics, such as occurs in elephantiasis, causes great lymphangiectasis with overgrowth of the subcutaneous connecting tissues; and the presence of lymphatics throughout practically all parts of the body suggests that there are

constituents of the lymph which are incapable of absorption by any other way than that of the lymphatics. That the lymphatics are not the *only* channel of absorption is shown by the results of numerous experiments which have been carried out on absorption by the blood vessels.

We know, for instance, that strychnine or other drug injected under the skin of a limb will exert its poisonous effects on the nervous system long before the drug itself appears in the lymph flowing from the limb, and therefore before it can have arrived by way of the lymphatics in the circulation. The very scanty lymph flow from a limb shows moreover that the ordinary interchanges between the living tissues and the blood (interchanges which involve oxygen and carbon dioxide as well as the foodstuffs and excreta of the cells), are carried out through the interstitial fluid without the intermediation of the lymphatics at all. Nor is the mechanism of these interchanges difficult to understand, in the case at any rate of most of the substances concerned. Our experiments on lymph production have shown that there is osmotic interchange between the extravascular and the intravascular fluids. Oxygen, carbon dioxide, diffusible substances, or water, will pass out of the capillaries in response to the ordinary osmotic differences. Thus we find a diminishing scale of oxygen tensions from red corpuscles to tissue cell, and a diminishing scale of CO_2 tensions from tissue cell to blood plasma. Strychnine introduced into the tissue spaces diffuses readily through the capillary wall into the circulating blood plasma.

A difficulty arises however in the case of the absorption of the normal interstitial fluid. We have evidence that the fluid in the tissue spaces may be taken up by the circulating blood directly, without intermediation of the lymphatics. What are the factors involved in this transference? This question may be investigated either by the introduction of

fluids into the serous cavities, or by examining the conditions of absorption of fluid from the connective tissue spaces of the body.

(1) *Absorption from the Serous Cavities.*—The serous cavities would seem to be especially adapted for investigating the mechanism of absorption of various fluids from the tissue spaces of the body. Like these they are in intimate relation with a terminal plexus of lymphatics, from which in many places they are separated merely by a thin layer of endothelium, although as Kollossow has shown, there is probably nowhere any direct communication between the serous spaces and the underlying lymphatics. The observations of Recklinghausen and others show that fluids as well as fine particles can pass with relative ease through the interstices between these endothelial cells, so that a fluid, such as milk, is rapidly absorbed from the peritoneal cavity by means of the lymphatics of the diaphragm.

This lymphatic absorption is not however the only method by which fluid may be taken up from the serous spaces. If, for instance, a soluble colouring matter, such as indigo carmine, or methylene blue, be introduced into the pleural or peritoneal cavity, it may appear in the urine within six minutes after the moment of injection, at a time when the lymph in the thoracic duct is free from colour, and there cannot have been sufficient time for any fluid absorbed by the lymphatics to have reached the circulation by way of the thoracic duct. There is in fact every facility for osmotic interchange between the blood in the vessels and the fluid within the serous cavities. A series of experiments which I carried out on the pleural cavity some years ago * show that absorption of fluid as well dissolved substances may take place by means of the blood

* Starling and Tubby, *Journ. of Physiol.*, XVI., 140, 1894.

TABLE I.—HYPERTONIC SOLUTIONS OF SODIUM CHLORIDE.

No. of experiment.	Duration of experiment.	Injected.			Recovered.			Absorbed.		Serum.	
		Volume in cc.	Per cent. NaCl.	△ of fluid.	Volume in cc.	Per cent. NaCl.	△ of fluid.	Volume in cc.	Grammes NaCl.	△	Per cent. NaCl.
1	30′	60	1·2	·72	61	·93		— 1	·163		
2	30′	80	,,	,,	83	·94		— 3	·18		
3	2°	60	,,	,,	57	·8		+ 3	·264		
19	30′	80	1·22	·74	85	1·03	·66	— 5	·10	·60	·68
20	30′	60	1·5	·91	64	1·21	·785	— 4	·13	·61	·72
4	30′	80	,,	,,	97	1·02		— 17	·21		·63
25	2°	80	,,	,,	95	·88	·61	— 15	·37	·595	·74
5	2°	80	,,	,,	94	·815		— 14	·44		·69
10	2°	80	,,	,,	90	·84		— 10	·44		·71

TABLE II.—HYPOTONIC SOLUTIONS OF SODIUM CHLORIDE.
0·5 PER CENT. NaCl. △ = ·34.

No. of experiment.	Duration of experiment.	Injected.		Recovered.				Absorbed.				Serum.	
		Volume injected in cc.	Weight of NaCl injected in grammes.	Volume in cc.	Per cent. NaCl.	Weight NaCl in grs.	△ of fluid recorded.	Volume in cc.	Grammes NaCl.	Fraction of volume injected.	Fraction of weight of salt injected.	△	Per cent. NaCl.
6	30′	80	·4	44	·72	·316		36	·084	·44		·615	·63
7	,,	50	·25	34	·69	·234		16	·016	·2		·61	·63
16	,,	80	·4	48	·71	·339	·53	32	·061	·4		·57	·66
18	2°	80	·4	56	·635	·355	·57	24	·045	·275		·64	
8	,,	80	·4	40	·75	·3		40	·1	·5		·575	·65
9	,,	60	·3	28	·69	·193		32	·107	·53		·565	·61
21	,,	80	·4	44	·71	·31	·60	36	·09	·45		·62	·67

TABLE III.—ISOTONIC SOLUTIONS. 1 per cent. NaCl. $\Delta = \cdot 61$.

No. of experiments.	Duration of experiment.	Injected.		Recovered.				Absorbed.				Serum.	
		Volume in cc.	Grammes NaCl.	Volume in cc.	Per cent. NaCl.	Grammes NaCl.	Δ	Volume in cc.	Grammes NaCl.	Fraction of volume injected.	Fraction of salt injected.	Δ	Per cent. NaCl.
12	30′	100	1·0	96	·963	·924		4	·076				·61
17	30′	80	·8	78	·915	·714	·595	2	·086			·595	·7
14	2°	80	·8	70	·8	·56		10	·24				·60

TABLE IV.—EFFECT OF SODIUM FLUORIDE.

No. of experiment.	Duration of experiment.	Injected.				Recovered.			Absorbed.		Serum.	
		Volume in cc.	Per cent. NaCl.	Per cent. NaFl.	Δ	Volume in cc.	Per cent. NaCl.	Δ	Volume in cc.	Grammes NaCl.	Δ	Per cent. NaCl.
13	2°	60	·952	·095	·68	50	·727		10	·21	·61	·59
22	2°	80	·39	·075	·315	40		·61	40		·585	
24	2°	80	·2	·2	·33	42	·66	·61	38	·11	·60	·645
11	30′	80	·5	·1	·395	60	·63	·605	20	·022	·60	·60

vessels, and that in this absorption there is no evidence of an active 'pumping' action by the cells either of the blood vessel wall or of the serous membrane.*

If a salt solution with a molecular concentration different to that of the blood-plasma be introduced into the pleural cavity, there is an initial passage of water into or out of the

* Leathes and Starling, *Journ. of Physiol.*, XVIII., 108, 1895.

cavity, according as the introduced fluid is hyper- or hypotonic to the blood-plasma. When isotonicity has been obtained by this means, the further interchange is chiefly concerned with an equalisation of the quantities of salts on the two sides of the absorbing membrane; but there is at the same time a slow absorption of the isotonic fluid from the pleura, about 5 cc. per hour, which can be ascribed partly to the lymphatics and partly to the colloid concentration of the blood, as we shall see shortly.

We found in these experiments that the results were not affected by poisoning the endothelium of the pleura either by means of sodium fluoride, or by the use of scalding water, in striking contrast to the effects of these measures, when employed in experiments on intestinal absorption. I give on pages 91 and 92 four Tables which show the course of the absorption when solutions of different strength are introduced into the pleural cavities with or without the addition of sodium fluoride.

(2) *Absorption from Connective Tissue Spaces.* — I have already dealt with the question of interchanges between the intravascular blood and the interstitial fluid of the tissues which are conditioned by differences of concentration in these two fluids, and we know that fluids of any description introduced into these spaces will slowly find their way into the lymphatics draining the part, especially if the transference be aided by active or passive movements of the part. Moreover, any rise of pressure in the capillaries tends to produce an increased amount of transudation, and therefore increased distension of the tissue spaces. The fluid which thus fills these spaces is practically identical with the blood-plasma, except as regards its protein content and any changes in its composition due to the metabolic requirements of the cells. Wherever we obtain tissue fluid for examination, or the lymph

coming from the tissue spaces, with the one exception of the liver, we find a protein content far inferior to that of the blood-plasma.

The interchange between blood and spaces, so far as regards the fluid, must be reciprocal; there must be a possibility for the fluid in these spaces to get back into the blood. What mechanisms are available for this re-absorption? Must all the interstitial fluid take the slow and devious path by way of the lymphatics and thoracic duct, or can it pass directly back through the capillary wall into the circulating blood? There is no doubt that the latter alternative is correct and that the fluid can be directly taken up from the tissue spaces into the blood circulating through the capillaries, without the intermediation of the lymphatics.

If an animal be bled to a large amount, the latter portions of the blood obtained differ from the earlier portions in that they are more dilute, the blood containing fewer corpuscles and the separated plasma a smaller content in protein. The fluid which has come into the blood and has effected its dilution is derived from the tissues, and the process represents an attempt on the part of the organism to make up the total volume of the circulating fluid to its normal amount. The drying of the tissues thereby produced is evidenced by the extreme thirst which ensues after any severe hæmorrhage and results in a greater uptake of water from the intestine, so that finally the total quantity of fluid, both of blood and tissues, is re-established, long before the organism has had time to make good the shortage in red corpuscles and plasma-protein.

This uptake of fluid from the tissues can be shown to be entirely independent of the gradual return of the tissue fluid to the blood by way of the thoracic duct. Artificial anæmia reduces the rate of flow from the thoracic duct, and

the dilution of the blood observed after hæmorrhage is not interfered with in any way by ligature of this duct. Moreover, the abdominal viscera are not directly or exclusively concerned in the process, since the dilution of blood as a result of hæmorrhage may be observed after a total extirpation of all the abdominal viscera. I have shown by direct experiments * that the blood circulating through the connective tissues can take up an isotonic fluid present in the meshes of these tissues. The experiment was carried out as follows:—

The blood of a dog was defibrinated *intra vitam*, by bleeding, whipping, and reinjecting the blood five or six times. (This was to avoid the danger of capillary clots during the subsequent experiment.) The dog was then bled to death, and cannulæ inserted in the femoral arteries and veins on both sides. The right leg was then made œdematous by the injection of 1 per cent. or 1·05 per cent. NaCl solution into the connective tissues by means of a needle. Part of the blood which had been obtained having been set aside for subsequent analysis, the rest was divided into two equal parts. One-half was then led through each limb at a pressure varying between 65 and 85 mm. Hg. By means of an arrangement of tubes and clamps, somewhat similar to that of Ludwig's 'Stromaiche,' it was possible, as soon as all the blood had been led through, to start the circulation afresh from the bottle which had been previously connected with the vein. I was thus carrying on two experiments (one of them being a control) at the same time. Each half of the blood was led through one leg from 12 to 25 times. The experiment was then stopped, and the solids in the whole blood and in the serum of the three samples of blood were estimated, as well as the relative amounts of hæmoglobin in each. It was found

* *Journ. of Physiol.*, XIX., 312, 1896.

that the blood, which had been led through the normal leg from 12 to 25 times, was either unaltered, or, in most cases, had undergone slight concentration. The blood, which had been led the same number of times through the œdematous leg, had in all cases absorbed fluid; both the whole blood and the serum were more dilute and the hæmoglobin percentage was diminished. In these experiments the freezing points of the blood serum and of the fluid injected to form the œdema were estimated, and care was taken to ensure that the osmotic pressure of the injected fluid was not below that of the blood-serum, so that the absorption of fluid could not be explained by ordinary osmotic processes. I give here Tables showing the results of these experiments.

	Solids of Blood per cent.			Hæmoglobin (standard = 100).	
No. of experiment.	Standard.	From normal leg.	From œdematous leg.	Blood from normal leg.	Blood from œdematous leg.
I.	21·00	21·08	19·98	—	—
II.	18·9	19·2	18·5	—	—
III.	22·2	22·2	21·4	—	—
IV.	lost	20·1	19·4	—	—
V.	20·6	(no control)	20·00	—	—
VI.	21·26	21·42	20·56	100	97
VII.	19·97	20·66	19·75	104	96
VIII.	20·7	21·2	20·00	103	95
		Two experiments with Serum.			
IX.	21·12	21·08	21·09	—	—
X.	19·5	19·9	19·7	102	102

Solids of Serum and Freezing Points.

Standard.	Normal leg.	Œdematous leg.	Composition of œdema fluid and freezing point.	No. of times blood transfused through legs.
—	6·6 per cent. $\Delta = -·635$	6·1 per cent. $\Delta = -·635$	1 per cent. NaCl $\Delta = -·610°C.$	12 times
—	—	—	1 per cent. NaCl	16 ,,
—	7·2 per cent. $\Delta = -·640$	6·7 per cent.	1 per cent. NaCl $\Delta = -·610°C.$	12 ,,
—	—	—	1·05 per cent. NaCl	12 ,,
—	—	—	1·05 per cent. NaCl	12 ,,
—	—	—	1·1 per cent. NaCl	20 ,,
—	8·28 per cent. $\Delta = -·64$	7·71 per cent. $\Delta = -·64$	1·1 per cent. NaCl $\Delta = -·660°C.$	24 ,,
$\Delta = -·600$	$\Delta = -·615$	$\Delta = -·63$	1·03 per cent. NaCl $\Delta = -·640°C.$	20 ,,
	Two experiments with serum.			
—	$\Delta = -·605$	$\Delta = -·605$	Ox serum. $\Delta = -·580°C.$	15 ,,
—	$\Delta = -·645$	$\Delta = -·635$	Ox serum. $\Delta = -·585°C.$	15 ,,

From these experiments, we may affirm with certainty that isotonic salt solutions can be taken up directly by the blood circulating in the blood vessels.

The Mechanism of Absorption.

We have now to consider how this absorption is effected. Are the capillary walls so constituted as to react to a lowering of the capillary pressure with an active absorption of the extravascular fluid, *i.e.*, is the absorption due to the vital activity of the cells? Or can we find mechanical conditions that will account for this absorption?

The first possibility that will strike anyone working at the subject is that the absorption, like the transudation of fluid, may be effected by a process analogous to filtration. Landerer* estimated the tissue tension at half to three-quarters of that existing in the capillaries. It is evident that, if such were the case, any considerable fall of intracapillary pressure would bring it below the tissue-pressure, and a back-filtration into the vessels might occur. Some experiments of Klemensiewiez,† with regard to the mechanical effects of œdema on the circulation, might be quoted against this hypothesis. This latter observer led fluid through a piece of intestine enclosed in an outer tube of glass. He found that at first there was transudation outwards through the intestinal wall and a rise of pressure in the glass tube. As soon however as the pressure in the outer tube reached that obtaining at the venous end of the model capillary, this latter collapsed. Exudation continued from the arterial end of the capillary. The pressure therefore rose higher and higher in the outer tube until the exuded fluid had caused collapse of the greater part of the intestinal tube. He concluded that a similar sequence of events would take place in œdema, and that the exuded fluid would tend to compress the veins, raising the pressure in the capillaries still higher and increasing the exudation. A vicious circle was thus established, which ended only with the complete arrest of the circulation through the part affected.

This objection of Klemensiewiez to the possibility of filtration backwards holds good only if the structural relations in the connective tissues are similar to the arrangement of his

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* "Die Gewebsspannung in ihrem Einfluss auf die ortliche Blut-und Lymph-bewegung," Leipzig, 1884.

† "Sitzb. der k. Akad. der Wissensch," LXXXIV., 1881, and XCIV., 1886.

mechanical model. If however the capillaries, instead of running freely through the connective tissue spaces, are bound to the walls of these spaces by an adventitia of radiating fibres, a rise of pressure in the spaces above that obtaining in the capillaries will not collapse these latter, but will rather tend to dilate them; and filtration back into the capillary would be structurally possible. If sections be cut of injected œdematous connective tissues, it will be seen that the capillaries are surrounded and supported by such an adventitia of radiating fibres, and have in fact a structure very similar to that figured by Ranvier* in the lymphatic gland and by Heidenhain † in the section through a villus. In the veins however, no such arrangement can be seen, all the fibres surrounding these tubes being apparently disposed concentrically. From a purely anatomical study, it would seem therefore that a filtration back into the capillaries is possible, provided that the rise of pressure in the tissue spaces does not extend to the tissues surrounding the larger veins. The question whether filtration back into the vessels is or is not possible from the connective tissues in most parts of the body can be only definitely solved by physiological experiment.

I found that, when fluid was injected into the connective tissues of the leg, the outflow from the veins of the leg diminished, showing that a rise of pressure in these spaces causes collapse of the big veins, and therefore increased pressure in the peripheral veins and capillaries (Fig. 8). Similar results were obtained on injecting fluid into the interstices of a muscular organ such as the tongue, or of a glandular structure such as the submaxillary gland; so we may conclude that absorption of fluid by the blood vessels by a process of

* "Technisches Lehrbuch der Histologie" (Nicati und Wyss), Fig. 208, 1877.

† Cp. "Quain's Anatomy," 10th ed., III., Pt. 4, Fig. 110.

backward filtration is impossible in the subcutaneous connective tissues of the limbs, in muscles, and in all glandular structures which have an analogous build to the submaxillary gland. Theoretically we may say that absorption by filtration is possible only in those regions of the body where a sudden rise in tissue-pressure will not be propagated to the neighbourhood of the large veins. Such regions might be found in the cutis itself or in the intestinal villus, but such

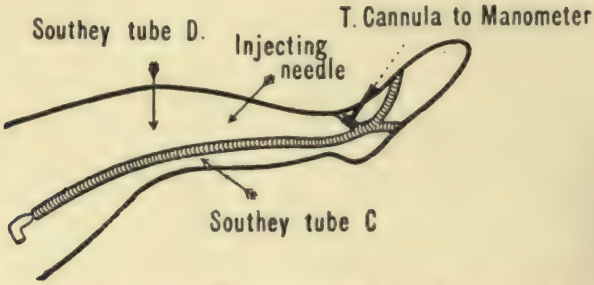

FIG. 8.—Diagram to show arrangement of experiment on absorption of fluid by the blood-vessels.

By the injecting needle fluid was injected into the subcutaneous tissue, and the pressure of the œdema fluid thus produced was measured by means of manometers attached to the two Southey's tubes (small perforated silver tubes).

The flow through the vein was measured by allowing the blood to drop from its proximal end on to a drop counter, while changes in the pressure peripheral to the œdema were determined by a manometer attached to a ⊥ cannula inserted into a vein of the foot.

minute spaces are not at present accessible to our experimental methods of investigation. So far as our results go, reabsorption by a process of back-filtration must be excluded.

There is however another factor present which would aid absorption of fluid by the blood vessels, and might therefore account for the reabsorption of the tissue fluid which occurs after hæmorrhage, or when the general blood pressure is lowered. In Lecture II. I called your attention to the fact that the non-diffusible constituents of the blood serum, chiefly

proteins, were capable of exercising an osmotic pressure or osmotic attraction for water, which amounted to about 4 mm. Hg. for every 1 per cent. protein in the serum. Blood-plasma with 6 to 8 per cent. proteins would therefore exert an osmotic pressure of 25 to 30 mm. Hg. as compared with an isotonic salt solution. The importance of these results lies in the fact that, although the osmotic pressure of the proteins of the plasma is so insignificant when contrasted with that of its saline constituents, it is of an order of magnitude comparable to that of the capillary blood pressure; and whereas capillary pressure is the chief determining factor in the production of interstitial fluid, the osmotic difference of pressure dependent on the greater concentration of the fluid within as compared with that without the blood vessels might be sufficient to determine absorption. In fact the osmotic attraction of the serum, or plasma, for the extravascular fluid will be proportional to the forces expended in the production of the latter, so that at any given time there may be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood for the surrounding fluids. With increased capillary pressure there must be increased transudation. The blood will become more concentrated until equilibrium is established at a somewhat higher point, when there is a more dilute fluid in the tissue spaces and therefore a higher absorbing force to balance the increased capillary pressure. With diminished capillary pressure there will be an osmotic absorption of salt solution from the extravascular fluid; this becomes richer in proteins, and the process will come to an end when the difference between its protein osmotic pressure and that of the intravascular plasma is equal to the diminished capillary pressure.

It is evident that this mechanism will not account for the absorption of serum, or other fluid rich in proteins, from the

serous cavities and connective tissue spaces. It is difficult however to get satisfactory evidence that such fluids are absorbed by the blood vessels. Serum, when injected into the pleural cavity, is absorbed with such slowness that it is impossible to exclude the possibility that the whole of the absorption has taken place by way of the lymphatics. In two experiments, in which I made the hinder limb of an animal œdematous by the injection of serum instead of salt solution (Cp. Table, p. 96), I could obtain no evidence of absorption of the œdema fluid by the blood vessels.

It ought to be possible to determine experimentally whether the mechanical processes which I have described suffice to explain the whole of the interchange between the blood and the tissues. I have indeed instituted certain experiments in this direction, but have not yet obtained sufficiently definite results on account of the complexity of the factors involved. It would seem however that the experimental test might be applied somewhat as follows :—

Absorption by the blood vessels as a result, say of artificial hæmorrhage, if determined entirely by the osmotic attraction of the plasma colloids for the extravascular fluid, can only bring about a passage of water and salts into the blood vessels. We know that after bleeding the blood-serum becomes more watery, *i.e.*, its proteins diminish. By ascertaining the total volume of circulating blood and the change in its hæmoglobin content after bleeding, as well as the relative proportion of corpuscles to plasma, we could find the absolute volume of the fluid which has passed from tissue spaces into blood vessels. According to my explanation this fluid should be pure salt solution. That it is more dilute than plasma is clearly shown by experiments, but our data do not yet suffice to decide whether the incoming fluid is a weak solution of protein, such as that contained in the tissue spaces, or is a pure salt

solution. If it is proved by quantitative results to contain protein, then some other factor, such as back-filtration or active absorption by the endothelial cells of the blood vessels, must be involved in addition to the attractive forces exercised by the colloid constituents of the circulating blood.

LECTURE VI

THE OUTPUT OF FLUID

For the normal functions of the body constancy of medium is essential. The maintenance of this constancy is determined partly by the regulation of the intake through the intermediation of the nervous system. The chief ganglionic masses of the organism have for this reason been aggregated especially at its mouth end, and their regulating power over the intake grows with the gradual increase in the complexity of their reactions coincident with their development into the brain of the higher animals. If we cut away the functions of appetite, which we may locate in the cerebral cortex, and probably in the deeper cells of this structure, the regulation of intake is largely interfered with.

The alimentary canal, apart from the nervous regulation of the oral aperture, has but little power of adapting its activities to the needs of the body as a whole. It is true that substances which may be regarded as more or less normal, *e.g.*, sugar and sodium chloride, are absorbed with greater facility than substances such as sodium sulphate or potassium iodide, which do not form necessary constant ingredients of the body. The difference is only one of degree, and the absorption of these substances themselves may continue, although there may be already a greater amount of them in the organism as a whole than it actually requires.

The injurious results of any indiscriminate activity on the part of the alimentary canal are counteracted by one of the chief organs which effect the output of fluid, viz., the kidneys.

Water is lost to the body by means of the lungs; water and dissolved substances by the skin. In neither of these cases is the output of water determined by the water balance of the body. The presence of aqueous vapour in the expired air may be regarded as an accident of the structure of the respiratory organs, and the output of water by this means is conditioned by the frequency and depth of respiration, and therefore by the needs of the organism for oxygen. The output of water by the skin represents a means by which the organism maintains a constant body temperature, and is determined entirely by the amount of heat produced in the body in relation to the temperature of the surrounding air. In the kidneys we find an organ whose function, broadly speaking, is the regulation of the amount and composition of the total fluid of the body: a regulation which it is able to carry out in consequence of its sensitiveness to minute changes in the composition and amount of the blood circulating through its vessels.

Thus in the normal individual the kidneys put out every day about 1,500 cc. of a fluid containing all the soluble waste products resulting from the nitrogenous metabolism of the tissues during the last twenty-four hours, as well as all the salts which have been taken up in the food and have passed through the body without being needed for storage in any growing tissue.

Since the concentration of urine may be many times higher than that of blood, its freezing point varying from 2° to 4° below zero, it is evident that a considerable amount of energy must be expended by the kidney in its production. Neither the concentration nor the composition of the urine is constant. In this fluid we find all the soluble waste products in whatever amount they have been produced. In it we find also any substances which have made their way into the blood through

the alimentary canal and are not required for the needs of the organism, as well as normal constituents of the body so soon as, for one reason or another, they accumulate in the blood above their ordinary concentration. The function of the kidney is to keep the composition of the circulating fluid constant, and we can therefore alter the urine in any direction according to the nature of the change which we bring about in the composition of the body. Thus the chief salt of normal urine is sodium chloride. If an animal be deprived of sodium chloride in its food, this salt practically disappears from the urine long before any change can be detected in the sodium chloride content of the plasma. If we drink large amounts of water, we do not produce any great lowering of the molecular concentration of the plasma, or any great increase in the volume of the circulating blood. As fast as the water is absorbed from the alimentary canal, it is picked up by the kidneys and passed out into the urine, which becomes extremely dilute with a molecular concentration far below that of the blood. The kidney therefore presents in the highest degree the phenomenon of 'sensibility,' the power of reacting to various stimuli in a direction which is appropriate for the survival of the organism: a power of adaptation which almost gives one the idea that its component parts must be endowed with intelligence.

When however we extend our investigations on the functions of these organs, we come across a whole set of conditions in which this intelligent adaptation suddenly makes default, in which the secretory activity of the kidney is apparently aroused by purely mechanical conditions without reference to or in direct opposition to the needs of the organism as a whole. Thus the injection of a concentrated salt solution, *e.g.*, 10 per cent. sodium sulphate, or sodium chloride, into the circulation produces a copious flow of urine which is not only

less concentrated than that of the injected fluid, but is less concentrated than the normal urine, although, by the injection of the salt solution, the molecular concentration of the body as a whole is increased. Change in the blood flow through the kidney may bring about alterations in the flow of urine quite irrespective of the composition of the blood or of the tissues.

The occurrence of these two classes of phenomena seems to be determined by the fact that the kidney is a dual organ, and that while one part of it acts, so to speak, passively in response to force impressed upon it from without, another part, endowed with sensibility, reacts to external forces in a direction which may be opposed to these forces, but is in all cases the appropriate one for the welfare of the whole organism.

This dual nature of the kidney's activity has formed the basis of all our views on the physiology of this organ, since its histology was first investigated by Bowman and by Ludwig, and attention was drawn to the marked differences in structure and arrangement of the glomeruli at the beginning of the renal tubules and of the cells lining the rest of these tubules. Such a marked difference in structure must determine difference in function, and it is therefore customary to treat separately the functions of the glomeruli and the functions of the tubules. Opinions as to the different parts played by these two sets of structures are still widely divergent, and we cannot expect to attain any general agreement among physiologists until some method shall have been devised for investigating the functions of one of them apart from the other. I may follow here the general custom and discuss the mechanism of the kidney's activity under these two headings.

Functions of the Glomeruli.—It is generally assumed, as the best explanation of known facts with regard to the secretion

of urine, that a dilute saline exudation free from protein is formed in the glomeruli and that it becomes concentrated on its way through the tubules either by the absorption of water and certain salts or by the secretion and addition of urea, uric acid, etc., as well as of such salts as acid phosphates.

As to the nature of the glomerular functions two opinions have been held. According to the Ludwig School the process is one simply of filtration, in which under the pressure of the blood in the glomerular capillaries the water and crystalloid constituents of the plasma are filtered through the glomerular epithelium, leaving behind the protein constituents. According to Heidenhain the process cannot be regarded as one simply of filtration but involves the secretory activity, *i.e.*, the doing of work on the part of the glomerular epithelium.

If the glomerular urine is a filtrate it must resemble blood-plasma in practically all particulars except its protein content, since the blood pressure, which is the only force causing filtration, is too small to effect any appreciable separation of salts. On the other hand, a certain minimum difference of pressure between the two sides of the membrane must be present in order to separate the colloids from the other constituents of the plasma. In an earlier lecture I have shown that 1 per cent. of proteins in the serum corresponds to about 4 mm. Hg. pressure, so that blood serum containing 7 to 8 per cent. of proteins would possess an osmotic pressure, due to its colloidal content, of 25 to 30 mm. Hg. In order to produce a filtrate, free from protein, from the blood-plasma circulating through the glomerular capillaries, a minimum difference of pressure of between 30 and 40 mm. Hg. will be necessary, *i.e.*, the pressure of the urine in the tubules and ureter must always be at least 30 mm. Hg. lower than the pressure of the blood in the glomeruli. A direct determination of the latter figures is not possible. But

the anatomical arrangements are such as to bring this pressure up to a high point. Not only are the vasa afferentia very short but their diameter is one-third greater than that of the vasa efferentia. Moreover the sudden increase of bed which ensues as the blood passes from vas afferens to the bundle of capillaries must itself cause a rise of pressure in the latter, due to the transformation of the kinetic energy of the moving fluid into the statical energy represented by pressure on the walls of the vessels.

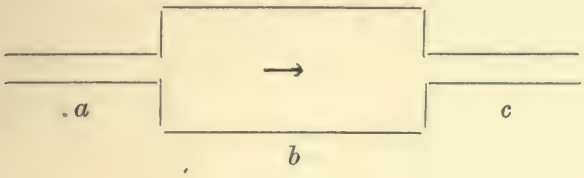

FIG. 9.

This point can be rendered clearer by the following considerations. If a fluid is flowing in a tube of continuous bore *a b*, there will be a continuous fall of pressure from *a* to *b*. If, however, in the tube *a b c* (Fig. 9) the segment *b* be of much greater diameter than the segments *a* and *c*, although, while the fluid is at rest, the pressures will be equal at all points of the system, as soon as the fluid moves from *a* to *c*, there is a fall of pressure between *a* and *c*, but a manometer attached to *b* may show an actually greater pressure than a manometer inserted at *a*. Apparently therefore fluid is flowing from the place of lower to a place of higher pressure. The apparent paradox is due to the fact that the energy causing the fluid to move from *a* to *b* is of two kinds. It equals $\frac{1}{2}\,mv^2 + P$, *i.e.*, is represented by the kinetic energy of the moving mass of fluid as well as the difference of pressure between any two points of the tube. The total energy will diminish continuously from *a* to *c*, and is used in overcoming the resistance of the system. We may say then that the sum of these two, namely, $\frac{1}{2}\,mv^2 + P$ is greater at *a* than *b*, and is greater at *b* than *c*. But as the fluid passes from the narrow tube *a* into the wide tube *b*, there is a sudden fall of its velocity and a consequent diminution of the factor $\frac{1}{2}\,mv^2$. In order then to provide for a *continuous* fall in the total energy of the fluid, namely, $\frac{1}{2}\,mv^2 + P$, the diminution in the factor $\frac{1}{2}\,mv^2$ must cause a corresponding increase in the factor P, *i.e.*, in the lateral pressure exercised by the fluid on the vessel wall. As the total diameter of the bed of the stream in the capillaries may be twenty times that of the bed in the vas afferens, the

velocity of the blood in these capillaries will be only $\frac{1}{20}$ of that in the artery, and the kinetic energy of the blood only $\frac{1}{400}$. It is possible therefore that the pressure exercised by the blood on the walls of the capillaries may be even greater than that in the interlobular arteries, and this effect will be still further aided by the narrow diameter of the vas efferens. Although the pressure in the ordinary capillaries of the body is probably not greater than 20 to 30 mm. Hg., the glomerular capillaries might present a pressure little inferior to that in the main arteries of the body.

The pressure in the ureter is under normal circumstances approximately nil, whereas that in the glomerular capillaries is probably not more than 20 mm. Hg. below that in the main arteries of the body, so that there is a difference of pressure on the two sides of the membrane more than sufficient to cause a constant filtration of a protein-free fluid from the blood-plasma coursing through these capillaries. On raising the pressure on the tubule side, the filtration ought to come to an end when the pressure approaches a figure which is within 30 to 40 mm. of that in the glomeruli. A number of observers have found that urinary formation comes to an end when the blood pressure falls to between 40 and 50 mm. Hg. In the same way the urinary secretion ceases if the pressure in the tubules be raised by means of ligature of the ureter. Under these circumstances it is found that urinary secretion continues for a time until the pressure in the ureter rises up to a certain point. In one experiment* the following pressures were obtained in a dog which was secreting urine copiously under the action of diuretin. Manometers were connected both with the carotid artery and with the ureters. The latter were then ligatured.

Arterial pressure.	Ureter pressure.
140	72
138	92
133	88

* Starling, *Journ. of Physiol.*, XXIV., 317, 1899.

In this experiment secretion came to an end with a difference of pressure between ureter and arteries of about 40 to 50 mm. Hg.

The absolute pressure attained within the ureter in any given experiment after ligature of this tube will vary with several factors. In the first place if the minimum secreting pressure is really conditioned by the colloid content of the blood-plasma, it will be less the smaller the proportion of colloids in the plasma. In one experiment* a flow of urine was observed with a blood pressure as low as 18 mm. Hg., but in this case the blood was extremely diluted as the result of the continuous injection into the blood vessels of normal salt solution.

On the other hand, the ureters, or at any rate the urinary tubules, cannot be regarded as absolutely water-tight. Not only are the cells of these tubules capable of taking up fluid, but it is probable that at high pressure a certain amount of actual filtration takes place between the cells. This process of re-absorption will tend to diminish the actual pressure of the fluid in the ureters, so that the secretion of urine may apparently come to a standstill when there is still a difference of pressure between blood and urine considerably over 50 mm. Hg. Under such circumstances the ureter pressure will be higher and the difference of pressure between urine and blood less, the more rapid the formation of urine by the glomeruli. In a number of experiments by V. E. Henderson† it was found that the figure B.P.—U.P. tended to approximate 40 mm. Hg. the more rapid the secretion of urine was. With a slow secretion the flow of urine apparently came to a stop when there was as much as 80 mm. difference of pressure on the two sides of the glomerular membrane.

We may conclude that for the production of any urine by the kidney a certain minimum difference of pressure is necessary between the blood in the glomeruli and the urine in the tubule, and that this difference becomes less the smaller the protein content of the blood. Since the only work required in the formation of a protein-free filtrate from the blood is that due to the osmotic pressure of the proteins themselves, and the observed difference of pressure during secretion is greater than this osmotic pressure, we are justified in concluding, provisionally at any rate, that the mechanical factors

* Gottlieb u. Magnus, *Schmiedebey's Archiv*, XLV. 248, 1901.

† V. E. Henderson, *Journ. of Physiol.*, XXXIII. 175, 1905.

present at the upper end of the urinary tubule are sufficient to account for the production of a glomerular transudate free from protein, but containing the same proportion of water and salts as the blood-plasma circulating through the capillaries.

If the process occurring in the glomeruli is simply one of filtration, three conditions must be realised.

(1) The amount of filtrate, so long as the ureter pressure is constant, must depend on the pressure and rate of flow of the blood in the glomerular capillaries, and must fall or rise with the latter.

(2) The constitution of the fully formed urine as it appears in the ureters, after modification by addition or subtraction on the part of the tubular cells, must approximate more closely to the supposed glomerular transudate containing the same proportion of salts as the blood-plasma, the more rapidly the formation of the glomerular transudate takes place: *i.e.*, the quicker the flow of urine, the more nearly must the composition, reaction, and osmotic pressure of the urine resemble that of the blood serum.

(3) The total quantity of solids excreted in any given time must be increased with any increase in the urinary flow. For whatever the activity of the tubules, the glomeruli must blindly turn out a certain proportion of solids with every cubic centimetre of fluid that they form.

We may deal first with the influence of alterations in the renal blood supply on the flow of urine. Ligature of the renal vein diminishes and soon stops the flow altogether. Since this procedure must cause a large rise of pressure in all the capillaries of the kidney, this result was regarded by Heidenhain as disproving any possibility of the glomerular process being of the nature of a filtration. At any given time however the glomeruli contain but little blood. With total cessation of the renewal of this blood, their contents

will rapidly become so concentrated that the capillaries will be practically filled with a mass of red corpuscles. No filtration of water and salts can take place unless there is a continual renewal of the fluid on the blood side of the filter.

On the other hand, alterations in the blood supply to the kidney, determined by changes on the arterial side, have pronounced effects on the amount of urine formed. The pressure in the glomerular capillaries and the rate of flow through these capillaries can be increased in either of two ways:

(*a*) By increase of the driving force, viz., the general blood pressure.

(*b*) By a diminution of the resistance to the flow of blood through the kidneys, as by dilatation of the vessels of this organ.

The results of the experiments carried out on these points can be represented in the following tabular form:—

Procedure.	General blood pressure.	Renal vessels.	Kidney volume.	Urinary flow.
Division of spinal cord in neck	Falls to 40 mm.	Relaxed	Shrinks	Ceases
Stimulation of cord ..	Rises	Constricted	Shrinks	Diminished
Stimulation of cord after section of renal nerves	Rises	Passively dilated	Swells	Increased
Stimulation of renal nerves	Unaffected	Constricted	Shrinks	Diminished
Stimulation of splanchnic nerve	Rises	Constricted	Shrinks	Diminished
Division of one splanchnic nerve:				
a. In dog ..	Unaffected	Dilated	Swells (?)	Increased
b. In rabbit ..	Falls	Relaxed	Shrinks (?)	Diminished
Plethora	Rises	Dilated	Swells	Increased
Hæmorrhage	Falls	Constricted	Shrinks	Diminished

It will be seen that in every case, where an increased blood flow attended with a rise of blood pressure in the glomerular capillaries is brought about, the urinary flow is at the same time increased.

Another factor, altering the ease with which filtration of watery fluid and salts through the glomerular capillaries would take place, would be the composition of the circulating plasma. Any dilution of this plasma must render filtration more easy, while a concentration would make it more difficult. As a matter of fact both hydræmia and especially hydræmic plethora, caused by injection of normal saline into the circulation, evoke an increased flow of urine. The same effect occurs when the plethora is caused by injection of defibrinated blood, though if the blood has been previously concentrated by depriving the animals of water, the flow so caused is but small.

A number of experiments, which have been carried out on the action of diuretics, have a close bearing on the question of the nature of the process occurring in the glomeruli. A large increase in the urinary flow can be brought about by the intravenous injection of salts, such as sodium sulphate, or potassium nitrate, or of neutral crystalloids such as urea or sugar. These bodies are often grouped together as saline diuretics. The question arises whether the chemical changes induced in the renal circulation by the intravenous injection of sugar and salt solutions are sufficient to account for the diuresis. There are three factors which might be concerned in promoting an increased glomerular transudation. These are :—

(1) A rise of pressure in the glomerular capillaries.

(2) Acceleration of the blood flow through the capillaries.

(3) Diminution of the amount of proteins in the blood-plasma.

When a concentrated solution of salts is injected into the circulation, the osmotic pressure of the plasma is raised and

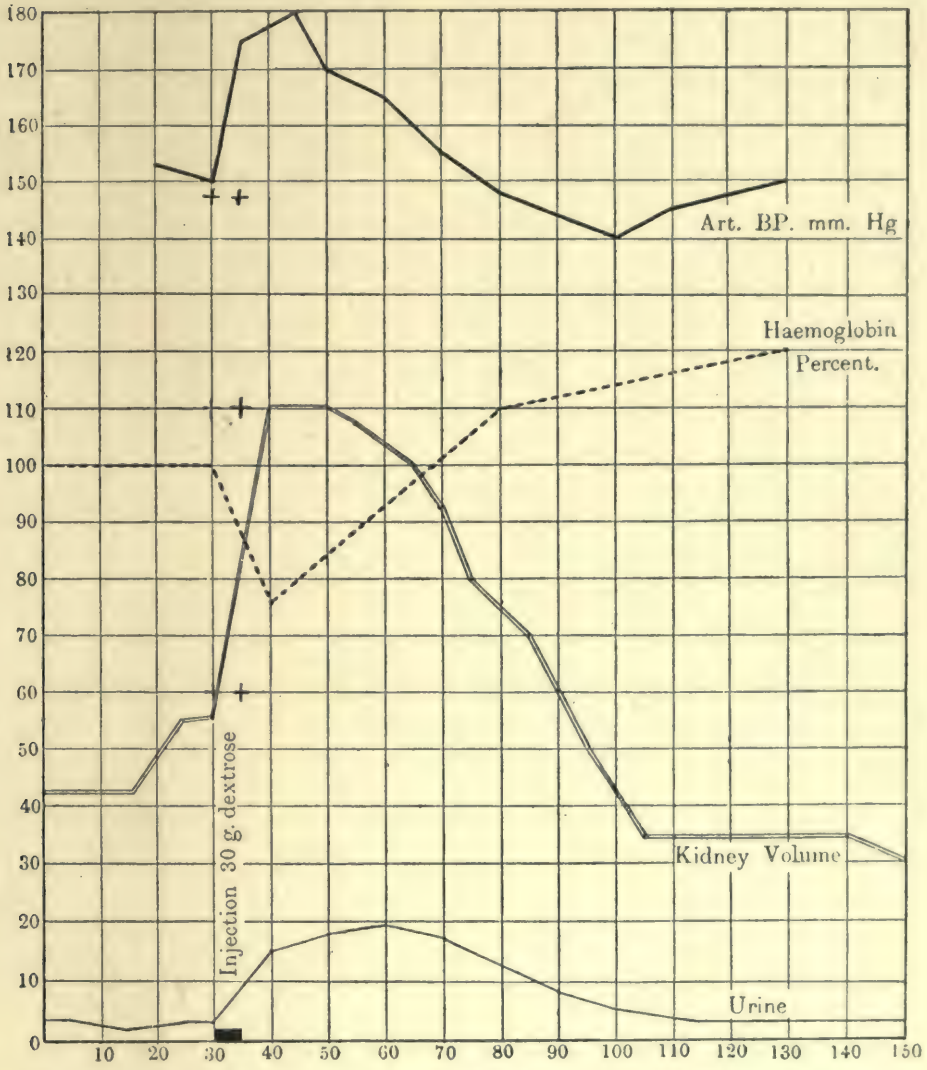

FIG. 10.—Curves showing effect of intravenous injection of a strong solution of glucose on the arterial blood pressure, on the volume of the circulating blood (as judged by the hæmoglobin percentage), on the volume of the kidney and on the secretion of urine.

there is at once a passage of water from the tissue cells into the blood stream, in consequence of the osmotic differences between the blood and cells so induced. As a result the

total volume of the circulating fluid is increased by the addition to it of water derived from the tissues, *i.e.*, a condition of hydræmic plethora is set up. The effect is the same as if a large bulk of normal saline fluid had been injected into the circulation. So long as this hydræmic plethora continues, so long is there a rise both in arterial and venous pressures and an increase in the velocity of the circulating blood. The kidney placed in an oncometer shows a great increase in volume. While the plethora lasts there are mechanical conditions at work in the kidneys, *i.e.*, increased pressure, increased rate of flow, and diminished concentration of plasma, all of which would concur in producing an increased glomerular transudation. With certain substances, such as sodium chloride, the diuresis is co-terminous with the hydræmic plethora; with others of this class, such as grape sugar, the diuresis outlasts the plethora, so that the continued increased secretion of urine leads to an actual concentration and diminution of volume of the circulating blood, as is shown in the Figure.

If the kidney be placed in an oncometer, it is found that the dilatation of the kidney outlasts the plethora and comes to an end only with the cessation of the increased urinary flow. Local influences therefore must be at work (perhaps the direct effect of the sugar on the blood vessels) which lead to an active dilatation of the renal vessels and a consequent rise of pressure and increased velocity of the blood in the glomeruli. That this vascular change is really responsible for the increased urinary flow is shown by the fact, determined by Cushny, that if the swelling of the kidney be prevented by means of an adjustable clamp on the renal artery, no diuresis is produced: so long as the kidney is kept at its normal size the flow of urine remains at the same rate as before.

With regard to the specific diuretics such as caffeine, the

question is not quite so clear. In most cases injection of caffeine in the rabbit brings about a dilatation of the kidney and a proportional increase in the secretion of urine. But cases have been recorded in which an increase in kidney volume occurred without increase in urinary flow, or on the other hand an increase in urinary flow without any increase in the kidney volume, or even in the rate of blood flow through the kidney (as determined by Brodie's method). The general rule however is that an increased blood flow is obtained *pari passu* with the increased urinary flow, and a consideration of certain peculiarities in the renal circulation must prevent us from laying too much stress on apparent exceptions to the rule. To the blood entering the kidneys by the renal arteries two ways are open. The blood may pass through the vasa afferentia, through the glomeruli and tubular capillaries, back to the renal vein. On the other hand, it may escape the glomeruli altogether and pass through the vasa recta directly into the interlobular capillaries and so into the renal veins. It is a common experience in injecting the blood vessels of the kidneys post-mortem to find the renal arteries, interlobular capillaries, and veins filled to distension with the injected mass, but hardly any injection in any of the glomeruli. One must assume in such a case that there has been spasmodic contraction of the muscular coats or of the vasa afferentia. The blood circulating through the kidney might therefore attain its normal extent and yet, on account of such contraction, no blood at all be flowing through the filtering apparatus, *i.e.*, the glomeruli. On the other hand, a dilatation of the afferent vessels and a slight constriction of the efferent vessels would cause a big rise of pressure in the glomerular capillaries and a consequent increased transudation, without necessarily altering to any marked extent the total circulation of blood through the whole organ. The changes in the afferent and

efferent vessels and the glomeruli are however beyond our control or powers of observation, so that it is impossible to devise at the present time any crucial experiment which might decide the nature of the process occurring in the glomeruli.

The Composition of the Urine.—If the glomerular function is that of mere filtration we should expect that, the more rapidly the process occurs, the more nearly would the urine, which is turned out into the ureters, resemble the blood-plasma in composition, reaction, and osmotic pressure, since the glomerular filtrate hurried through the tubules would have very little time to undergo any changes resulting in its concentration. If, on the other hand, the diuresis produced by salt or sugar solutions is to be ascribed to a stimulation of the renal epithelium, we should expect the differences between blood-plasma and urine to be greatest at the height of the diuresis, when the specific stimulant is present in the blood in largest amounts. The following experiment shows that, the more rapid the secretion of urine, the more closely does its concentration, as indicated by its osmotic pressure and depression of freezing point ($\triangle$), approximate that of the blood-plasma. A dog received 40 gms. of dextrose dissolved in 40 cms. of water. The Table opposite represents the relative concentrations of urine and blood serum at different stages in the diuresis thereby produced.

A still nearer approximation of the concentration of the urine to that of the plasma was obtained by Galeotti * in some experiments, in which the modifying influence of the tubular epithelium on the glomerular transudate had been prevented by poisoning the animal with corrosive sublimate, which causes destruction of the epithelium but is said to leave the glomeruli intact.

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* *Archiv. f.* (*Anat. u.*) *Phys.*, 200, 1902.

Since the glomerular transudate must have a concentration approximately identical with that of the blood-plasma, it would be impossible for a urine formed by mere filtration to have a concentration less than that of the blood-plasma. It is however of frequent occurrence that after copious potations of tea or light beer, urine is passed with an osmotic pressure and a molecular concentration considerably below that of the blood. In one case Dreser* obtained a urine with a freezing point of $\Delta = 0{\cdot}16°$ C., and the same result has

Time.	Urine.	Rate of flow.	Δ of Urine.	Δ of blood serum.
11.30—12	10 cc.	3·3	2·360	·625 (at 12.0)
From 12.0 *to* 12.7 *injected* 40 *grms. dextrose into jugular vein.*				
12.7 —12.15	35 cc.	45	1·210	
12.16—12.20	20 cc.	50	0·975	·700 (at 12.16)
12.20—12.30	52 cc.	52	0·835	
12.30—12.40	45 cc.	45	0·825	·700 (at 12.30)
12.40—12.50	22 cc.	22	0·830	·675 (at 12.40)
				·675 (at 12.50)

been obtained on one or two occasions when the diuresis has been produced by the administration of caffeine. If we assume that this hypotonic fluid is formed by the glomeruli, we must at once give up any idea of the process in these structures being essentially one of filtration. In dealing however with the functions of the tubules, we shall see that there is definite evidence of the possession by their epithelium of a secretory power for water as well as for solid constituents. The fine adaptation of the kidney to slight changes in the

* Schmiedeberg's *Archiv*, XXIX. 303, 1892.

composition of the blood is apparently an endowment of the tubular epithelium, and in those cases, where large quantities of hypotonic urine are passed, there is not at any time any appreciable change either in the composition of the blood or in its total volume. Water is absorbed from the alimentary canal and is almost immediately excreted by the kidneys. When we attempt to produce the same effect by infusion of large quantities of water or hypotonic solutions into the blood stream, we get a flow of urine apparently determined entirely by the circulation through the kidney and having a concentration not inferior to that of the blood. The passage of hypotonic urine can be ascribed to a modification of the glomerular transudate as it passes through the tubules, a modification due partly to the absorption of salts from the fluid, partly, perhaps chiefly, to a secretion of water or extremely dilute salt solutions by the cells of the tubules themselves.

Certain other observations accord with our hypothesis that in Bowman's capsule a fluid is transuded having the same molecular concentration as blood-plasma, and therefore considerably less concentrated than normal urine. Ribbert succeeded in extirpating the whole of the medullary portion of the kidney in the rabbit, leaving the cortex intact, and found in this case that during the survival of the animal the urine that was passed was much more dilute than normal. In cases too where there is destruction of the tubular epithelium, while the glomeruli remain intact, either in consequence of disease or, as in Galeotti's experiments, as a result of poisons, we are accustomed to obtain a dilute copious urine, and the continual passage of such urine is in man regarded as a sign of one form of renal disease.

The experimental facts which we have passed in review do not therefore negative the view that the glomerular epithelium plays the part of a passive filter in the formation of urine, and that the energy of the process by which urine is produced in Bowman's capsule is entirely furnished by the heart in producing the blood flow through, and the blood pressure in,

the glomerular capillaries. Before coming to any conclusion however as to the importance to be ascribed to this function in the formation of urine, we must turn our attentions to the functions of the greater part of the kidneys, namely, the tubules.

Functions of the Renal Tubules.

Whatever the nature of the glomerular activity it is evident that the multiform epithelium of the tubules may alter the glomular transudate, either by the absorption or by the secretion of water or solid constituents. We may deal with the evidence for the occurrence of these two processes separately.

Evidence for Secretion by the Urinary Tubules.—Although it is impossible to collect the secretion of the glomeruli apart from that of the tubules, the arrangement of the blood vessels in certain animals enables us to influence separately the circulation to these two parts of the kidney. The amphibian kidney receives a blood supply from two sources. A number of renal arteries leaving the aorta pass into the kidney and supply the whole of the glomeruli, the vasa efferentia from which pass, as in the mammalian kidney, into the intertubular capillaries. These are also supplied with blood of venous character by the renal portal vein. If the whole of the renal arteries be divided or ligatured, the glomeruli, as was shown by Nussbaum, are entirely cut out of the circulation, though the tubules continue to receive venous blood through the renal portal vein.

Nussbaum stated that the ligature of all the renal arteries caused cessation of the urinary secretion, which could be re-induced by injection of urea. He therefore concluded that urea with water was secreted by the tubules, whereas peptone, sugar, and hæmoglobin were turned out by the glomeruli.

Beddard * showed however that these results of Nussbaum's must have been due to the fact that he had not obstructed the whole of the renal arteries. One or two of these small vessels will suffice to supply blood to a considerable area of the glomeruli of the kidney. He found that, after complete obstruction of the arteries, no urinary flow could be induced even with subcutaneous injection of urea. But the cutting-off of the arterial blood supply from the tubules caused a rapid destruction of the tubular epithelium, so that one could not take the result of the experiment as negativing the possibility of this epithelium having, when in a normal state of nutrition, some amount of secretory power. He therefore carried out with Bainbridge † another series of experiments of the same description, in which the frogs, after ligature of the renal arteries, were kept in an atmosphere of pure oxygen. Under these circumstances sufficient oxygen diffused into the blood of the renal portal vein to maintain an adequate supply of oxygen to the tubules. No desquamation of the epithelium resulted, and injection of urea produced a small flow of urine even when, by subsequent injection of the blood vessels, it was proved that every glomerulus had been cut out of the circulation. Similar results have been obtained by Brodie and Cullis § in certain experiments in which oxygenated Ringer's fluid was led through the surviving kidney of the frog. A small flow of urine was obtained, especially after urea or potassium nitrate had been added to the fluid. The quantities of urine obtained in these two sets of experiments were too small to admit of a proper analysis or of a comparison of their molecular concentration with that of the blood serum of the animal.

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* *Journ. of Physiol.*, XXVIII., 20, 1902.

† *Biochemical Journal*, I., 255, 1906.

§ *Journ. of Physiol.*, XXXIV., 224, 1906.

The definite evidence thus afforded of the possession of a secretory function by a certain portion at any rate of the tubules is borne out by a histological examination of these structures under various conditions of activity. In the cells of the convoluted tubules various kinds of granules and of vacuoles may be distinguished. Gurwitsch divides these vacuoles into three classes :—

(1) Large granules staining densely with osmic acid, and probably rich in lecithin ;

(2) Smaller very numerous granules consisting of some form of protein material ;

(3) Large vacuoles lying close to the free margin of the cells whose contents do not undergo coagulation with the ordinary fixing reagents, and therefore are free from protein, fat, or mucin. These vacuoles are especially marked in kidneys, which are secreting at a great rate in consequence of the injection of saline diuretics or of large quantities of normal salt solution. They are probably to be regarded as excretory vacuoles and as representing water or saline fluids which have been collected by the cells and are being passed on by them to the lumen of the tubules.

As a rule it is impossible to trace any definite constituent of the urine on its way through the cells of the tubules. If however a solution of uric acid in piperazin be injected intravenously into a rabbit, the kidneys, taken 20 to 60 minutes after the injection, present tubules full of uric acid concretions. In the medullary portion of the kidney this uric acid precipitate is confined to the lumen of the tubules, but in the convoluted tubules granules of uric acid are to be found in the epithelial cells, especially towards their inner borders. Since these cells are able to excrete uric acid when present in abnormal quantities in the blood, it is a reasonable assumption that they also undertake the secretion of this substance

under normal conditions. Certain observers have in fact described the presence of urate granules in the cells of the convoluted tubules of the bird's kidney.

Although the larger number of the urinary constituents must escape detection on their way through the cells, we can throw some light on the excretory functions of the kidney by studying the mechanism by which it excretes certain dye-stuffs, such as sulphindigotate of soda or indigo carmine. If the indigo be injected into the veins, after section of the cord to stop the urinary flow, and the animal be killed half an hour later and the kidneys fixed with absolute alcohol, although no urine has been obtained in the interval the kidneys are found to be of a bright blue colour. On cutting into the kidneys the colour is seen to be confined to the cortex, and on making microscopic sections granules of the pigment are found within the lumen of the convoluted tubules and also in the cells lining these tubules. It has been suggested by several physiologists that the appearances after the injection of indigo are due, not to the secretion, but to the absorption of water in the convoluted tubules. A certain amount of the dye-stuff is thus rendered visible by becoming more concentrated, and is precipitated in a granular form as soon as the salt concentration of the fluid reaches a certain height. The fact that these appearances are wanting after the injection of ordinary carmine, which stains the glomeruli as well as the tubules, combined with the histological facts mentioned in the last paragraph, render this a somewhat forced explanation; and we must take the results of the injection of indigo carmine as telling rather in favour of a secretory than of an absorptive function on the part of the convoluted tubules.

The question as to the secretory activity of the kidney can be attacked from another side. The glomerular filtrate can only contain those crystalloids of the blood which are diffusible

and are not closely combined with its colloidal constituents. Löwi has shown that in this connection a contrast is to be drawn between the behaviour of substances such as urea or sodium chloride and certain other constituents of the blood such as phosphates or sugar. Any increase in the rate at which the glomerular secretion takes place must cause a corresponding increase in the total amount of the solid diffusible constituents of the blood-plasma which are turned out within a given time. Thus every diuresis increases the total output of chlorides and of urea. It is worthy of note that under normal circumstances a diuresis, caused for example by drinking large quantities of water, does not increase the total output of phosphates in a given time, nor does it increase the very small amount of sugar which is normally excreted by the kidneys. If however phosphates be present in the blood in an unattached condition, as, for instance, in consequence of previous injection of sodium phosphate into the blood, then any diuresis increases the amount of phosphates put out in a given time. The same thing holds for sugar. If an excess of free uncombined sugar be present in the blood either in consequence of intravenous injection of this substance or as a result of previous extirpation of the pancreas, any form of diuresis will increase the rate at which it is turned out by the kidneys. Löwi concludes therefore that phosphates, which must be present in minimal quantities in the glomerular transudate, are for the most part secreted by the activity of the cells of the convoluted tubules. Under normal conditions, *e.g.*, as after administration of phloridzin, the cells of the kidneys can be excited to a similar activity with regard to sugar. After phloridzin injection the urine contains considerable quantities of sugar, but the rate at which the sugar is secreted is not affected in any way by raising the rate of urinary secretion (*e.g.*, by the injection of such substances as

sodium sulphate, which increases the rapidity of the glomerular process of transudation).

Evidence of Absorption by the Renal Tubules.—The experiments of Ribbert, mentioned above, in which removal of the medullary portion of the kidney led to the formation of an increased quantity of more watery urine, points to the possession by the tubules of a power of absorbing water. We have other evidence that this power of resorption is not confined to water, but may affect also the dissolved constituents of the glomerular transudate. It was pointed out by Meyer that, if two salts such as sodium sulphate and sodium chloride were present at the same time in the glomerular transudate, any process of resorption should affect chiefly the more diffusible salt, namely, sodium chloride. Such a differential resorption would account for the much greater diuretic power of sodium sulphate as compared with sodium chloride. In certain experiments Cushny * produced a diuresis by the injection of equal parts of equivalent NaCl and Na_2SO_4 solutions into the veins of a rabbit. An increased flow of urine was produced, which lasted two-and-a-half hours. The chlorides of the urine rose with the diuresis and reached their maximum at the height of the urinary flow. They then sank, and in some experiments had practically disappeared altogether from the urine towards the end of the observation. The concentration of the sulphates however continued to rise in the urine to the end of the experiment. Thus, in the first of two identical experiments, when the rabbit was killed at the height of the diuresis, the serum contained ·547 per cent. chlorine and ·259 per cent. sulphate, while the urine contained ·372 per cent. chlorine and ·546 per cent. sulphate. In the second, in which the rabbit was killed when the rate of the urinary flow had

* *Journ. of Physiol.*, XXVII., 427, 1901.

considerably diminished, the serum contained ·493 per cent. chlorine and ·191 per cent. sulphate, while the urine contained ·094 per cent. chlorine and 2·0 per cent. sulphate. These results are illustrated by the accompanying Figure

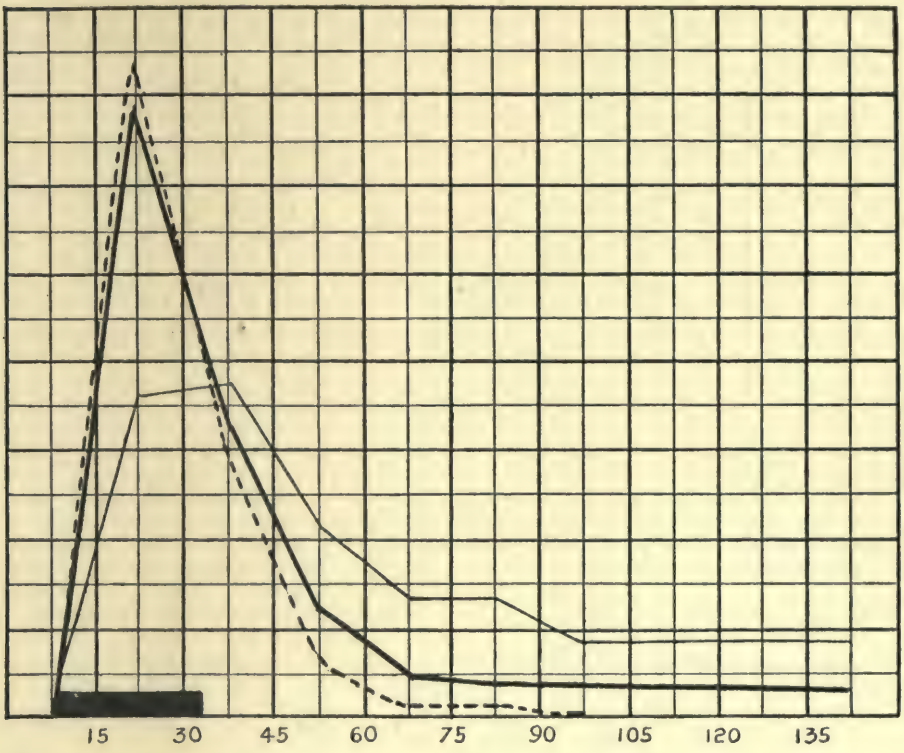

FIG. 11.—Curves showing excretion of urine (heavy unbroken line), of sulphate equivalents $\left(\frac{SO_4}{96}\text{, light line}\right)$, and of Cl equivalents $\left(\frac{Cl}{35{\cdot}5}\text{, broken line}\right)$, after injection of 50 cc. of a solution containing 1·775 gr. Cl and 4·8 gr. SO_4 per 100 cc. The heavy line along the base shows the duration of the injection.

(Fig. 11), showing the excretion of sulphates and chlorides in a rabbit after injection of 50 cc. of a solution of the sulphate and chloride of sodium.

The difference between the two salts can be made still more striking if the process of resorption be augmented by increasing the pressure within the tubules by partial obstruction of one

ureter. Thus in one experiment, where diuresis was produced by the injection of 30 cc. of a solution containing 5·85 per cent. NaCl + 14·2 per cent. Na_2SO_4, the right ureter was partially clamped so as to make the right kidney secrete against a pressure of 30 mm. Hg. The following results were obtained:—

—	—	Urine cc.	Cl. g.	SO_4 g.
4.37 till 4.47	Left kidney	24	0·0809	0·1080
	Right kidney	8	0·0142	0·0667
	Difference (absorption)	16	0·0677	0·0413

We must conclude that the tubular epithelium possesses the power of modifying the glomerular transudate, not only by the absorption of water, but also by the absorption of dissolved constituents, and that the relative permeability of the cells to these constituents is at any rate one factor in determining the substances absorbed. It is not however the only factor. The function of the kidney is to preserve the normal constitution of the body fluids by turning out those substances which are abnormal or present in too great an amount. The behaviour of the tubule cells with regard to any given substance will therefore depend to a certain extent on the previous nutritive history of the body. If for instance the body is overloaded with sodium chloride, in consequence of the administration of large quantities of this salt to the animal during the few days preceding the experiment, the salt itself becomes an abnormal constituent, and the kidney secretes a urine far richer in sodium chloride than is the blood-plasma. Moreover when diuresis is produced in such an animal by the injection of equivalent quantities of sodium chloride and sodium sulphate, there is no diminution of the

NaCl in the urine towards the end of the diuresis, but its percentage rises steadily as the rate of urinary flow diminishes. On the other hand a total deprivation of sodium chloride extending over several days, although not altering to any large extent the percentage amount of this salt in the blood-plasma, leads to a total disappearance of the salt from the urine, the whole of the sodium chloride present in the glomerular transudate being absorbed on its way through the urinary tubules.

It has been suggested that the effects of certain diuretics on the kidney, such as caffeine, diuretine, or theocine, may be largely conditioned, not so much by their influence on the glomerular circulation, as by a paralytic effect on the absorptive functions of the tubules. According to Loewi * on injection of caffeine or diuretine, the increase of total amount of urine is not accompanied by any diminution in the percentage amount of NaCl. Perhaps however the strongest evidence in this direction is afforded by an experiment of Pototzky.† A rabbit had been fed on a diet almost totally devoid of chlorides and was therefore excreting a urine containing only 0·08 per cent. NaCl. Under the influence of diuretine the urine was increased and the concentration of the NaCl rose to ·64 per cent. The same increase in the percentage amount of sodium chloride in the urine has also been observed after the injection of theocine, which has therefore been specially recommended as a diuretic in cases of dropsy, where a diminution of the salt content of the body is a valuable means for the diminution of the dropsical fluid present in the tissue spaces.

What conclusions can we draw from this mass of experimental data as to the functions of the kidney as a whole, and

* Schmiedeberg's *Archiv*, XLVIII., 416, 1902.

† Pflüger's *Archiv*, XCI., 588, 1903

as to the part played by its various constituent elements in the secretion of urine? The amazing adaptability of its functions to the needs of the organism has been abundantly illustrated in the facts with which we have dealt. Its ordinary activity is determined by the production, as a result of the normal processes of metabolism, of soluble non-volatile substances in every cell of the body. These substances, together with the excess of water taken in with the food above that lost by respiration and cutaneous transpiration, are turned out by the kidney as urine. The activity of this organ must therefore be aroused in the first place by chemical stimuli. It must react to the slightest deviation from normal of the blood composition, by excreting water or dissolved substances. This delicate sensibility is displayed in two directions:

(1) Under the influence of certain substances, such as urea, uric acid or water, the cells of the convoluted tubules take up the substance, which is in excess, from the surrounding lymph and accumulate it in vacuoles, which are discharged on the inner surface of the cells into the lumen of the tubules.

(2) Besides this specific secretory activity of the cells of the convoluted tubules, the tubules as a whole are endowed with the power of absorbing both water and dissolved substances from the fluid in their lumen. Whether this absorptive power is limited to the cells of Henle's loop, as was first suggested by Ludwig, or occurs coincidently with secretion in the cells of the convoluted tubules, as might be imagined from the close analogy between the structure of these cells and that of the intestinal epithelium, we have not sufficient evidence to decide. We do know however that the quality of the absorption is strictly regulated according to the needs of the organism, so that the constituents, which are precious, are reabsorbed for service in the body, while those which are in excess or are of

no value to the organism, are allowed to pass out into the ureters. The process of resorption is indeed, as is shown by Cushny's experiments, largely dependent on the physical qualities of the substances undergoing absorption, and especially on the permeability of the renal cells to these substances. The physical conditions are however subordinated to the physiological, so that a salt so diffusible as potassium iodide is left in the fluid, while sodium chloride may be reabsorbed in large quantities.

The necessity for the endowment of the tubular epithelium with a resorptive as well as a secretory function is determined by the presence at the beginning of the tubule of a mechanism —the glomerulus, which is in all probability devoid of the fine selective power or chemical sensibility possessed by the cells of the convoluted tubules. The production of urine by the glomerulus is apparently regulated entirely by the pressure and velocity of the blood through its capillaries and by the colloid content of the blood-plasma. We may assume that in Bowman's capsule there is, under normal conditions, a constant production of a fluid free from protein but having the same crystalloid concentration as the blood-plasma. With any rise of general blood pressure, the amount of this transudate is increased; with any fall it is diminished. The small qualitative changes which are constantly occurring in the blood, as the result of the taking of food or the activity of different organs, probably produce but little effect on the amount of glomerular fluid. Only indirectly, as the result of their influence on the general blood pressure, or possibly in consequence of the production of substances having a vaso-dilator effect on the renal vessels, will the amount of the urine turned out by the glomeruli be affected. These structures therefore have the two-fold function of regulating the total amount of circulating fluid and of providing an indifferent

fluid, which will, so to speak, flush the kidney tubules, and carry down any constituents excreted in a concentrated form by the cells of these tubules.

The constant production of a glomerular transudate might result, especially in terrestrial animals, in the loss to the organism of water, or, under certain nutritive conditions, of indispensable constituents of the serum, such as sodium chloride, in amounts which could not be made good at the expense of the food. It is for this reason that an absorptive mechanism, sensitive to and reflecting the nutritive condition of the whole body, especially as concerns water and salts, is needed in the tubules. As the result of the complementary processes of absorption and secretion in the tubules, the unchanging glomerular filtrate undergoes great modifications in its passage towards the ureter. It receives urea, uric acid, phosphates, and under certain conditions, water, from the cells of the convoluted tubules. It gives up salts, especially sodium chloride, and generally water to the same or other cells of the tubules. So that finally, instead of a fluid isotonic with the blood and containing only about ·1 per cent. urea, we have a fluid of deep yellow colour, with a molecular concentration four or six times greater than that of the blood, and containing between 2 and 3 per cent. urea.

We have at the present time no means of judging the relative amounts of fluid furnished respectively by the glomeruli and the tubules to the fully formed urine. It is probable that, under ordinary circumstances, the processes of secretion and absorption of fluid go on *pari passu* in the urinary tubules just as they do in the mucous membrane of the small intestine. The demonstration of secretory powers in the cells of the convoluted tubules relieves us from the necessity of the assumption, made by Ludwig, as to the quantity of fluid normally turned out through the glomeruli. On the

hypothesis that the sole function of the tubules was one of absorption, and that all the urinary constituents were derived from the glomerular transudate, 30 litres of fluid would have to be filtered through the glomeruli, in order to excrete the 30 grms. urea, which is the daily output of a man. Of these 30 litres, 28 litres would have to be reabsorbed in the tubules. Since the amount of blood flowing through the two kidneys in a man probably varies between 1,600 and 1,800 litres in the 24 hours, there would be no difficulty in the production of such an amount as 30 litres, which would only represent a concentration in the blood in its passage through the glomeruli of under 2 per cent. The secretion and reabsorption of such large quantities of fluid seems, however, a clumsy way of arriving at a urine, whose composition should be adapted to the needs of the animal, and, as we have seen, the occurrence of an actual secretion of urea by the cells of the tubules takes away the necessity of assuming any such wasteful proceeding. It is probable that the actual amount of the glomerular filtrate in the 24 hours may not exceed to any large extent the actual amount of urine formed by the whole kidney in this time.

LECTURE VII

THE FLUID BALANCE OF THE BODY

Under normal circumstances the various mechanisms that we have discussed in the preceding lectures work together for the maintenance of an *average* quantity and composition of the internal media of the body. Not, however, constancy of amount and composition. Constancy of any bodily condition is unattainable in the presence of the varying conditions of our environment, and is indeed not compatible with our conception of life. Not only must there be deviations from the average in respect to the total volume and molecular concentration of the fluid of the body, including in this term the blood, lymph, and tissue fluids, but we may expect also to find variations in the distribution of these fluids, any one of them being increased or diminished at the expense of the others.

In order to get some idea of the interplay of the mechanisms concerned in the regulation of the body fluids, we may deal first with the manner in which the organism reacts to changes artificially induced in the total quantity of its fluid: changes greater, as a rule, than those occurring under normal circumstances, but on that very account presenting greater facilities for study and analysis. We can bring about such changes in the total fluid by adding to or abstracting from the circulating blood, and thus study the reaction of the organism to plethora or to anæmia.

Plethora.

A large increase in the volume of the circulating blood may be produced by the introduction of 200 or 300 cc. of

defibrinated blood from a dog into the veins of another animal of the same species. No evil effects follow such injection unless the volume of the blood introduced is very large in comparison with the total volume of the circulating blood in the animal receiving the injection. There is however a reaction on the part of the animal to the injection, which affects the mechanical conditions of the circulation, and secondarily the lymph production and the output of fluid, as well as the metabolism of the body as a whole.

The first effect of the injection, if into a vein, is to increase the diastolic filling of the heart and its output into the arterial system. On this account the arterial pressure rises. The whole mechanism of nervous vascular control is however directed towards the maintenance of normal arterial pressure, and by this means a constant flow of blood through the vessels of the brain. A rise of arterial pressure induced by increased filling of the heart brings about a reflex dilatation of the arterioles and therefore a difference in the distribution of pressure within the vascular system. The arterial pressure is thus maintained at a height differing but little from that of the normal pressure, while the venous pressure rises and the greater quantity of the injected fluid is accommodated in the big veins, whose capacity is largely increased by this rise of pressure. The increased venous pressure involves increased diastolic filling of the heart. The output of this organ is therefore increased. Since the arterial pressure is rather above than below normal, the work done by the heart at each beat must be also increased.

The resistance in the arterioles being diminished, the output from the arteries is increased in direct proportion to the increased output from the heart, *i.e.*, there is a large rise in the velocity of the blood through both the arterial and the capillary systems. In the dilatation of the big veins, which

enables them to accommodate the greater part of the excess of fluid in the vascular system, an important part is played by the liver which, in spite of its apparent rigidity, is extremely distensible. An enormous swelling of this organ may be produced by connecting the inferior vena cava with a long tube, so that the liver vessels can be injected backwards at a pressure of about double the normal, the portal vein of course being ligatured. After the production of plethora, while the greater part of the injected fluid is still in the vascular system, the liver increases very greatly in size, and it has been suggested that we may regard the liver to some extent as a safety cistern, as an organ which can take up blood in its meshes when there is any rise of pressure on the venous side of the heart, so that the latter organ is saved from the consequences of over-distension during diastole and therefore from overstrain and possible failure.

The fluid that has been introduced does not long remain in the blood vessels. If a cannula be inserted into the thoracic duct, plethora is found to be associated with a large increase in the lymph flow, and this increase may be taken as representing an increased transudation in the abdominal organs into the tissue-spaces, and through them into the lymphatics. There is in fact, as a result of the rise of capillary pressures, an increased leakage of the fluid constituents of the blood-plasma, which is especially marked in the abdominal viscera. Evidence of this leakage is afforded by an examination of the blood a quarter of an hour after the injection. The hæmoglobin- as well as corpuscle-content is found to have largely increased, showing that the greater part of the fluid of the defibrinated blood, which was introduced, has already escaped out of the vascular system, leaving behind the blood corpuscles and a certain proportion of the proteins of the plasma.

The rise of capillary pressure occasions also a more copious glomerular transudation, and therefore an increase in the excretion of urine. The extent of this increase differs according to the composition of the blood which has been injected. If it is already poor in water, the increased urinary flow may be minimal, and in any case comes to an end or becomes inappreciable before the total fluid, which has been added to the body, has been eliminated. This is not surprising in view of the fact that the leakage of fluid from the blood vessels causes a rise in the concentration of the plasma as well as in the relative proportion of red blood corpuscles, so that the force requisite to bring about filtration in the renal glomeruli must be increased in like measure.

The concentration of the blood, resulting from the leakage of the fluid into the lymphatic tissue spaces, raises the viscosity of this fluid, and therefore the resistance to its flow through the capillaries. If the injection be very large, this resistance may prove too much for the heart; the systolic volume of this organ becomes larger and larger, so that more and more blood accumulates behind it in the big veins and liver, and its distension increases between each beat; finally the over-dilated heart is unable to effect any onward movements of the blood at all, and the animal dies. Bleeding the animal under these circumstances brings about a rapid restoration of the heart's functions and a disappearance of all dangerous symptoms.

If we use normal saline fluid instead of defibrinated blood for the production of plethora, we obtain a condition known as hydræmic plethora, in which the total circulating fluid is increased, but the relative proportion of the blood corpuscles is diminished, and the protein-content of the plasma is also below normal. Under these circumstances the organism very rapidly rids itself of the excess of fluid. The watery plasma escapes with extreme ease into the tissue spaces and into the

lymphatics. The blood with its lower viscosity passes readily through the dilated arterioles and capillaries, so that the

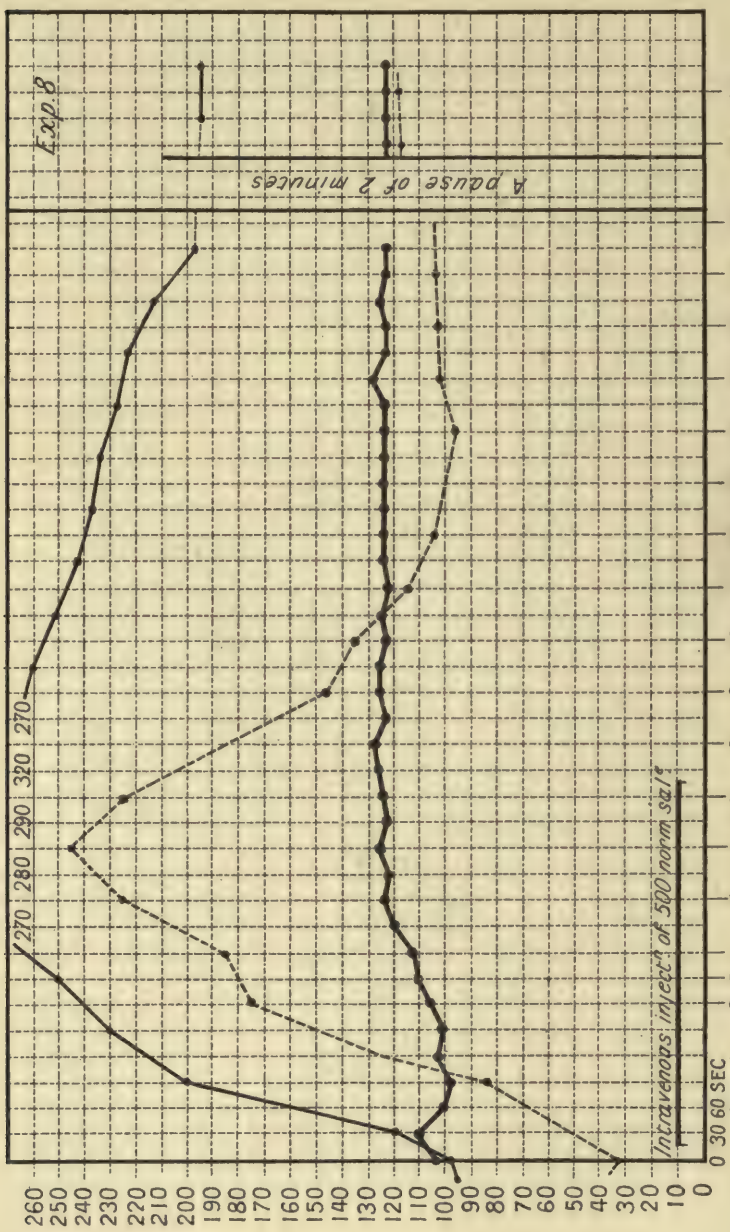

FIG. 12.—Course of the pressures in the portal vein (thin line), inferior vena cava (dotted line), and the carotid artery (thick line), after intravenous injection of 500 cc. normal saline fluid.

velocity of the blood-flow may be easily increased from six to ten times. The kidney swells enormously, and the rapid renewal of the blood in its vessels provides for a rapid filtration

of the water and salts of the dilute plasma through the glomeruli. Thus in most cases there is an enormous increase in the lymph flow from the thoracic duct as well as in the secretion of urine, which in each case lasts just so long as the pressure remains above normal in the capillaries concerned.

The course of the pressure in different parts of the vascular system after a large injection of normal salt solution is shown in the accompanying diagram (Fig. 12). Owing to the greater ease with which the salt solution is eliminated from the circulating blood, and the absence therefore of concentration of this fluid, we may inject huge quantities into the circulation without bringing about heart failure. Indeed, if the injection be carried on slowly, the kidneys tend to secrete at the same rate as the salt solution is allowed to flow into the jugular vein.

Anæmia.

By anæmia I mean a diminution in the total volume of the circulating blood, involving loss both of plasma and of corpuscles, such as may be brought about by bleeding the animal. Some of the effects of such a procedure have already been studied in connection with the phenomena of absorption by the blood vessels. As regards the mechanical conditions of the circulation, loss of blood by hæmorrhage has exactly the reverse influence to that produced by plethora. The guiding principle here, as there, is the need of the ruling tissues of the body for a constant supply of oxygen, and therefore for the maintenance of a normal blood supply through the brain. Owing to the absence of vaso-motor control of the intracranial blood vessels, this is accomplished through the intermediation of the arterial pressure. The whole aim of all the mechanisms set in action by change in the volume of the circulating fluid is the maintenance of this pressure. Loss of blood is therefore followed by constriction of the

arterioles. The flow through all the capillaries, except through those to the brain, is diminished, the pressure in these vessels is also diminished, and there is a fall of pressure in the great veins opening into the auricles as well as in the portal vein. The arterial side of the circulation is kept filled, so far as possible, at the expense of the venous side. The fall of pressure in the capillaries of the portal system and in those of the liver causes a diminution in the flow of lymph from the thoracic duct. In the same way the urinary flow may be diminished or abolished.

More important is the rapid emptying of the tissue spaces into the blood vessels, the mechanism of which we have already discussed. As a consequence of this passage of fluid from tissue spaces directly back into the blood vessels, the volume of the circulating fluid is increased towards normal. It is worthy of note that this passage is almost immediate, so that if we bleed an animal, say to 300 cc., the last 50 cc. of blood may be appreciably more dilute than the first 50 cc. The dilution of the blood brought about in this way is however limited. Comparative estimates of the composition of the circulating fluid from determinations made five minutes after bleeding and twenty minutes after bleeding show that the process is practically complete at the first period. Moreover, a second and third bleeding evoke only slight further changes in the concentration of the blood.

In studying the alterations in the composition of blood brought about by bleeding, it is necessary to take precautions against the disturbing influence of local variations. Where we are dealing with anæsthetised animals, the fall of pressure consequent on the anæsthetic may have already brought about a maximum passage of fluid from tissue spaces into blood, so that it is not possible to evoke any further dilution of the blood as the result of bleeding. In animals such as the

horse, where sedimentation of corpuscles occurs easily, the most incongruous results may be obtained. In consequence of the passage of blood, concentrated by sedimentation, into the general circulation after the bleeding, we may indeed obtain an apparent concentration of the whole blood instead of the expected dilution.

In the normal animal the process of absorption of the tissue fluids creates in all the tissues a need for more fluid, which, in the presence of the higher nervous system, is interpreted as thirst. The intake of the fluid by the intestines is therefore increased. Thus the process of dilution of the blood proceeds, first at the expense of the tissue fluid and then at the expense of the fluid absorbed from the gut, until the dilution of the plasma is sufficiently advanced to make up the total volume of circulating blood to normal. When this has occurred, the secretions of lymph and of urine resume their normal course, and indeed are rather more pronounced than before on account of the greater ease of transudation of the more watery plasma.

A considerable time, days or weeks, may elapse before the blood attains the same constitution as it had before the bleeding. Of the seat and mode of formation of the plasma-constituents we know nothing. The loss in red corpuscles is made up by increased activity of the blood-forming tissue in the bone marrow, and there seems every reason to believe that the stimulus to this increased activity of the marrow is to be found in the reduced oxygen tension of the blood passing through this tissue. Each unit volume of the blood carries less oxygen than would be carried by a blood containing the normal percentage of hæmoglobin, so that the amount of this gas and its tension must be diminished more rapidly as the blood flows through the tissue than would be the case under normal circumstances. The influence of lack of oxygen in exciting activity of the bone marrow has been demonstrated

in various ways. In the first place we have the real hypertrophy of the blood which occurs as the result of continued residence in high altitudes, *i.e.*, at low oxygen tensions. A similar effect to bleeding can be brought about by cutting out of function a certain proportion of the red corpuscles, as, *e.g.*, by partial poisoning with CO gas. It has been shown by Nasmith and Graham* that a condition of plethora, or at any rate an increased formation of red corpuscles and of hæmoglobin, may be induced in animals by chronic poisoning with this gas.

It is important therefore to remember that any factor, which tends to diminish the oxygen tension of the circulating blood, will tend to produce at the same time increased formation of red corpuscles and of hæmoglobin. As a result of bleeding however, we get not merely increased production of corpuscles. In all probability the stimulus is also effective on those tissues of the body which are engaged in building up the proteins of the plasma, so that one may speak of bleeding as affording a stimulus to the whole of the assimilative functions of the body, which is analogous in almost all respects to that experienced as the result of residence in high altitudes. Zuntz† and his school have shown that the effects of mountain air are apparent, not only in their influence on red corpuscles, but also on the nitrogenous metabolism of the body as a whole, so that there is in most individuals a positive nitrogen balance, an actual reproduction of the conditions found in the growing organism. We are thus literally correct when we speak of the rejuvenating effects of a holiday spent in the mountains. Before the application of steam and other agencies to the facilitation of methods of transit, which has occurred

* *Journ. of Physiol.*, XXXV., 32, 1906.

† See especially "Hohenklima und Bergwanderungen," by Zuntz, Loewy, Müller, and Caspari. Berlin, 1906.

during the last century, this rejuvenating effect was obtained by the practice of bleeding, the beneficial results of which had been discovered empirically. The blood-letting in the spring and at the fall called into play those recuperative processes of the organism which we now seek to stimulate by a trip to Switzerland or to the Rockies. It is probable that, with the recognition of the physiological effects of loss of blood, the practice of occasional blood-letting may be restored to the position of honour which it held in medical practice before it had been discredited by its employment as a panacea for all forms of disorder.

The mechanisms, which determine the adaptation of the organism to changes in the total volume of its fluid content, must come into play with every rise or fall in general blood pressure. Thus any marked alteration in the local distribution of the blood must bring about changes, not in the total volume of the body fluid, but in the distribution of this fluid between the blood and the tissues. The blood pressure of man is continually varying. The normal systolic pressure in the brachial artery, when the man is at rest, is about 110 mm. Hg. The slightest excitement or concentration of attention may increase this pressure by 20 or 30 mm., and in active exercise there may be a rise of blood pressure to between 150 and 200 mm. Hg. due, partly to the mechanical influence of the muscular and respiratory movements on the circulation, partly to mechanical stimulation of the medullary centres by metabolites produced in the contracting muscles.

How will such a rise affect the distribution of fluid? It has been pointed out that violent exercise, such as sprinting one hundred yards, will raise the corpuscle content of the blood 10 or 15 per cent. According to Oliver, every rise of pressure brought about by exercise of short duration causes a concentration of the blood and an increase of the fluid in the

tissue spaces of the finger. A similar temporary rise of pressure may be produced in an animal by injection of adrenalin. According to Hess,* such a rise causes a concentration of the blood in the veins of the body, but no change in the blood of the arterial system. This author therefore concludes that the lost fluid is made up to the blood in its passage through the lungs. I have been unable to obtain evidence of any such regulating function of the lungs. In every case a rise of pressure evoked by the injection of a small dose of adrenalin causes a concentration of the blood in the arteries as well as in the peins.

On the other hand, a fall of pressure, however produced, whether by chloroform narcosis, by heart failure, or by section of the spinal cord, causes a dilution of the blood by the same mechanism as that involved in the making up of the volume of the circulating fluid which occurs after bleeding. The same condition may be brought about by altering the distribution of blood within the body. Thus obstruction of the inferior vena cava above the liver causes increased concentration of the blood below the obstruction and a large increase in the lymph production within the liver. The plasma of the blood circulating through the rest of the body, *i.e.*, in a sample taken from the carotid or femoral artery, is found to be more dilute than at the beginning of the experiment. Lowering of pressure therefore causes passage of fluid from the tissue spaces into the capillaries; raising the arterial pressure causes increase of tissue fluid at the expense of the plasma.

Almost every observer has described a sudden increase in the relative number of corpuscles of the blood as the result of removal to high altitudes, or diminution of the tension of the oxygen in the blood. There seems to be little doubt that this

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* Schmiedeberg's *Archiv*, LXXIX., 128, 1903.

immediate increase of corpuscles, which is too sudden to be accounted for by increased activity of the blood-forming tissues, must be ascribed to a diminution of the plasma of the blood, accompanied perhaps by a corresponding increase of the fluid in the connective tissue spaces. The cause of this change in the blood is not yet understood. It might be accounted for if the increased arterial pressure recorded by some observers as the result of removal to high altitudes were a constant phenomenon, but I myself have been unable to find any appreciable change in the normal pressure on removal from the plains to the mountains.

On the other hand, the processes, which we have been considering, play an important part in determining the course of events in cases of heart disease (especially in cases where there is failure of compensation), and are responsible for many of the consequences or concomitants of such a disorder. The use of the heart-pump is to maintain a constant passage of blood from the venous to the arterial side of the vascular system; taking it from the former at a low pressure, it pumps it into the arterial system at a high pressure. Any failure of the pump ought therefore to tend to equalisation of pressure on the two sides of the system, *i.e.*, to a fall of arterial and a rise of venous pressure. Such a change in the pressures can be shown to be produced when the heart's action is interfered with by stimulation of the vagus, or by the injection of fluid, such as oil, into the pericardium so as to diminish the diastolic expansion of the heart. Since engorgement of the veins and a weak fluttering pulse are frequently observed in heart disease when there is failure of compensation, it was assumed by Cohnheim,* and more or less accepted by most clinical pathologists for many years, that the condition in such disorders

* Cohnheim's "Lectures on General Pathology" (New Syd. Soc., 1889).

is exactly comparable to that which may be produced in the laboratory by the injection of oil into the pericardium. In this case, as soon as sufficient oil has been introduced to interfere with the normal diastolic expansion of the heart, the pressure is seen to fall in the arteries, and to rise in the veins. At a certain point where interference with the heart's action becomes dangerous for life, even in the morphinised animal, there is a very sudden rise of venous pressure, especially marked in the portal vein, brought about by the anæmic stimulation of the vasomotor centres and the universal vascular constriction thereby produced.

Only within recent years has the applicability of the analogy with experimental conditions been put to a test by actual measurement of the arterial pressure in cases of heart disease. A series of observations of this description was made by Dr. H. J. Starling* on cases in the Norwich Hospital. The surprising fact was elicited that in no case of heart disease, however severe the symptoms and however marked the failure of compensation, was the blood pressure in the arteries below the normal. Only just before death occurred was a gradual fall of pressure to be observed. In fact, as he has shown, we may divide cases of heart disease into two classes: those in which the arterial pressure is normal; and those, chiefly occurring in older subjects, in which the pressure is very high and may amount to over 200 mm. Hg. In the latter class, it is probable that we must ascribe to the rise of pressure itself the production of lesions in the heart muscle and the ultimate failure of its action.

But the question arises: why does not failure of the heart-pump bring about a fall of arterial pressure? Why is it that in cases of heart disease we find a normal arterial pressure,

* H. J. Starling, *Lancet*, Sept. 29, 1906.

even when there is considerable over-distension of the veins? The responsible factor in determining the state of things has already been mentioned. The whole vascular system is subordinate in its activity to the needs of the master tissue of the body, viz., the brain. For these needs a certain height of arterial pressure is essential in order that the medullary centres shall receive a proper supply of blood and of oxygen. Whatever the working capacity of the heart, the brain will insist on having its proper supply of blood, failure of this for a short time being followed by the death of the animal.

What then is the result of temporary failure of the heart-pump? We have some clue to this in the experiment already described on the injection of oil into the pericardium. As soon as the arterial pressure falls so low as to cause an ischæmia appreciable by the vasomotor centre, the latter at once sends down by all the vascular nerves impulses which bring about universal vaso-constriction. If this is not sufficient to raise the arterial pressure, increased respirations and expiratory convulsions occur, and tend to force the blood from the veins into the heart, thereby increasing the output of the latter. Of course, in the experiment under consideration, an increased output is impossible, since we have artificially prevented the heart from receiving during diastole more than a certain small quantity of blood. The effort however to get the blood from the venous into the arterial side is present, and will be effective if the heart failure is brought about, not by distension of the pericardium, but by diminished emptying of the heart in systole.

Let us consider first the reaction of the heart to a sudden increase in the demands made upon it. If both splanchnic nerves be stimulated with a strong current, a large increase in the resistance to the outflow of the blood is at once produced. By enclosing the heart in a plethysmograph we may record

its behaviour under these conditions. The first effect is that the emptying of the heart is less effective. Its systolic volume is increased. The rise of pressure however determines also a rise of pressure on the venous side, and during diastole the heart receives more blood, in addition to the quantity of blood which it contains at the beginning of diastole, as the result of partial failure in previous systole. Its diastolic volume is therefore also increased.

For the next two or three beats the heart dilates with each beat, being unable to expel its contents against the high arterial pressure, and the dilatation is favoured by the fact that at the beginning of each systole the heart contains more blood than under normal circumstances. The increase in diastolic distension acts however as a direct stimulus to the heart muscle, increasing its capacity for work, while the high arterial pressure quickens the flow through the coronary arteries and therefore in this way also improves the capacity of the heart muscle. As the result of the improved nutrition and the increased excitation, the output of the heart at each beat continually increases, and after about half a dozen to a dozen beats we find that the expulsive effort of the heart is so successful that it attains its previous systolic volume, although it is putting out an increased amount of blood at each beat (Fig. 13).

The heart therefore finally reinforces the constriction of the arterioles in maintaining the high arterial blood pressure. If the vagi are intact, this recovery of the cardiac systolic volume may be hindered, the heart itself automatically and reflexly trying to spare its activities. If a valve be damaged in a normal heart, we generally find that the compensation, determined by the increased diastolic filling of the affected cavity, is so complete that practically no change occurs in the arterial pressure. The heart does more work, and in time its muscle-fibres become hypertrophied. If this increased

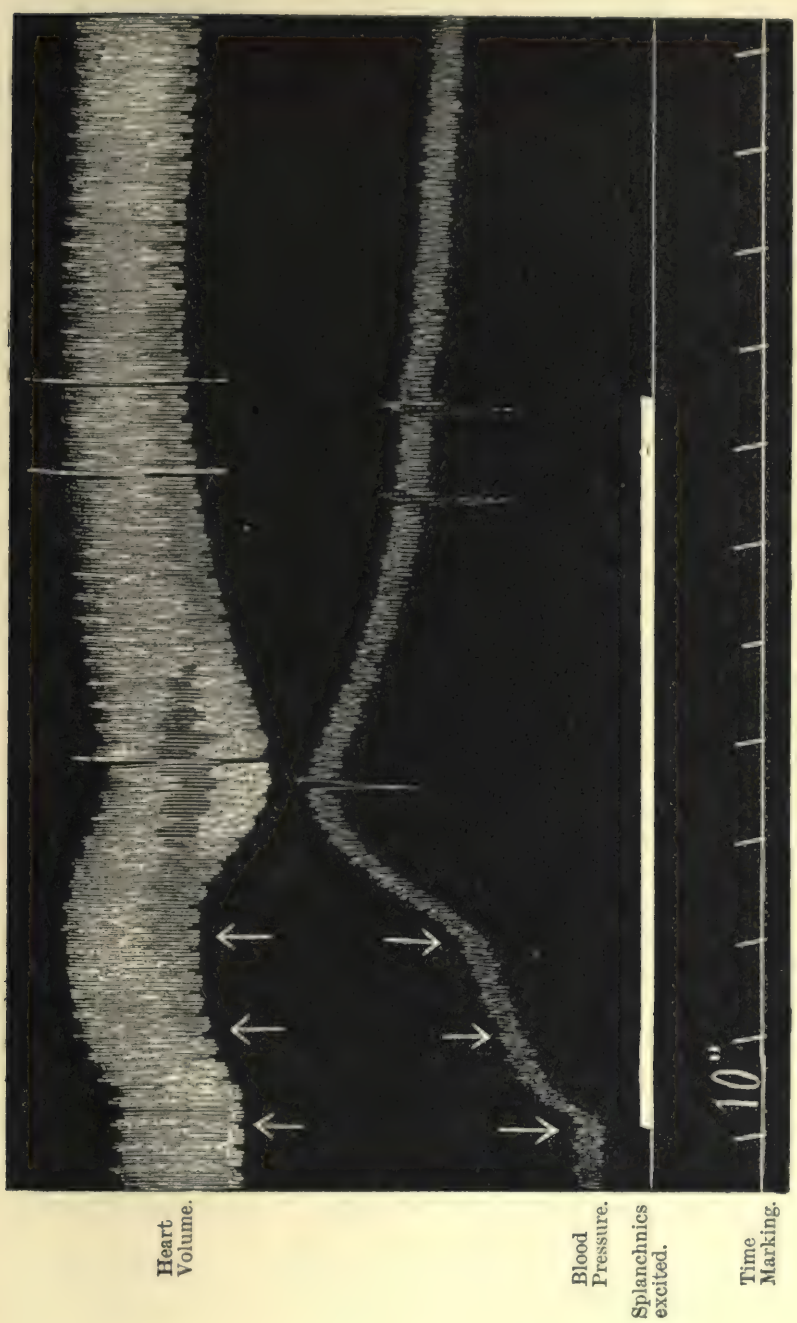

FIG. 13.—Curve showing the effect of a sudden rise in the arterial resistance on the output and volume of the ventricles. Systole causes a downward movement of the lever. The lower border of the white tracing represents the systolic volume, the upper border the diastolic volume.

work be interfered with by simultaneous change in the heart muscle, as may occur in rheumatic myocarditis, we may imagine failure of compensation occurring for some

little time. How will the organism react to such failure? Every failure of the heart-pump tends to bring about a lower arterial and a higher venous pressure. The heart wall therefore becomes more and more distended during diastole until the extra stimulus applied by the distension is sufficient to equalise the output of the heart to its intake during diastole. The maintenance of an adequate output involves therefore a continuance of the high venous pressure, which can only be secured simultaneously with the maintenance of a normal arterial pressure by the universal vascular constriction. The condition indeed is analogous, in the arteries and capillaries, to that produced by bleeding, although in the case of heart failure the vascular system is bled into the veins and cardiac cavities instead of the blood being lost to the body as a whole. Now every lowering of arterial pressure, and especially of capillary pressure, causes increased absorption from the tissues. The constriction of the vessels of the splanchnic area may be expected (though this is not yet proved), to enhance the rate of absorption of water from the alimentary canal, while the lowered pressure in the renal capillaries and the diminished rate of flow will lessen the output of fluid from the body. Finally therefore the necessary increased diastolic filling of the heart brought about by a rise of venous pressure, but associated with the normal arterial pressure demanded by the brain, can be maintained only by increasing the intake as compared with the output of fluid by the body as a whole. The total volume of circulating fluid must be increased.

We might therefore expect to find that a condition of hydræmic plethora would be set up. Clinical investigation in cases of heart disease or failure of compensation does not however reveal increased dilution of the blood, such as we might expect if the foregoing argument were correct or

complete. Although in some cases a relative paucity of red corpuscles may be found, in many others the hæmoglobin content of the blood is normal, or even somewhat increased. This might have been prophesied if we had taken into account another factor, which is the determining condition for the production of red corpuscles. The activity of the red bone marrow can be excited by any change in the animal which lowers the tension of the oxygen in the blood coming to this tissue, whether it be diminution of the total amount of hæmoglobin, such as that produced by bleeding, or exposure of the animal to atmospheres with deficient oxygen tension. In cases of partial heart failure, the arterial pressure is kept up only at the expense of the escape of blood from the arterial to the venous side, a slowing which is felt all round the system and affects the total circulation time. Moreover in many cases there is actual interference with the functions of the lung in consequence of the engorgement of its vessels. Cyanosis, *i.e.*, deficient aeration of the blood, is therefore a constant symptom of deficient cardiac action. Chronic cyanosis must have the same effect as chronic poisoning with CO gas, or exposure to an atmosphere of low oxygen tension, viz., a direct excitation of the function of the bone marrow and increased production of red corpuscles. We have thus, in failure of compensation, a combination of factors, one set of which determines an increase in the fluid constituents of the blood, the other set an increase in the red blood corpuscles. As the result a condition of real plethora is set up; and the vascular system contains an excess of blood of normal concentration and composition.

In the case of anæmia by hæmorrhage we found that the diminution in the tissue fluid, which was the immediate effect of the bleeding, was rapidly made good in a healthy animal by increased intake of fluid as compared with the

output. On the day after the bleeding the animal would already possess a normal blood pressure, as well as a normal state of distension of its tissue spaces. The same thing must occur in the case of failure of compensation. The disturbed balance between intra- and extra- vascular fluid is rapidly made good, so that finally the sole factors which we have to take into account are those of intake and output of fluid. The amount of fluid in the body will continue to increase so long as the heart is inefficient, and the condition of plethora will persist even when the balance between the intra- and extra- vascular fluid begins to be upset in the opposite direction, viz., in the production of increased transudation. Thus in many cases the patient finally becomes waterlogged. Not only is the volume of the circulating fluid increased, but all his tissues are filled to distension with dropsical fluid, in the production of which the increased filling of the vascular system as a whole must play an important part.

It is now many years since I pointed out that the physiological factors at work in failure of compensation must finally determine a true plethora, and the existence of this plethora has been in late years directly demonstrated by Lorrain Smith* with the aid of Haldane's carbon-monoxide method. Moreover it is only by the existence of an increased filling of the vascular system that we can account for the co-existence of a normal arterial pressure with distension of the veins throughout the whole body, and a rise of pressure within these vessels. In my next lecture we shall have to consider in greater detail the manner in which the distension of the tissue spaces with fluid, *i.e.*, the dropsy of heart disease, is brought about.

Among the factors determining the production and absorption

* Trans. Path. Soc. LIII., p. 136, 1902.

of tissue fluid, considerable importance must be attached to chemical changes in the tissues or in the blood, and such chemical changes must also be assumed to play a part in the determination of alterations in the total fluid content of the body both in health and in disease. Our knowledge of these factors is, however, much more scanty than is the case with the mechanical conditions which we have just been considering. The general character of their influence will be evident from a study of certain conditions which may be experimentally produced. Let us take, for example, the effects of increasing the crystalloid content of the blood by the injection of a concentrated solution into the blood stream. If a solution of 30 grs. of glucose in about 30 cc. of water be injected into the jugular vein, the first effect is a great increase in the volume of the circulating blood, brought about by the osmotic attraction of water into the vessels at the expense first of the tissue spaces, but ultimately of the tissue cells. The consequence of the hydræmic plethora thereby induced is increased circulation through the kidneys and increased output of urine containing large quantities of sugar. The sugar has a direct influence on the kidney vessels, or possibly on the kidney cells, so that the diuresis endures long after the total volume of the circulating blood has been restored to normal. Finally, when the flow of urine slows down, the blood has been concentrated to a point considerably above normal. Under ordinary circumstances the concentration of the tissues thus induced would produce intense thirst and increased intake of water, so that the urinary flow would be maintained at a high level until the whole excess of the glucose had been excreted.

Similar effects would be induced with injection of sodium sulphate. When sodium chloride however is injected into the blood vessels, it escapes with such ease into the tissues

that the total hydræmic plethora produced is less than with injection of glucose or sodium sulphate. Moreover this salt appears to exercise little or no specific influence on the kidney vessels or cells, so that the diuresis comes to an end as soon as the hæmoglobin content of the blood, and therefore its volume, has been restored to normal. On the other hand, the greater molecular concentration of the tissues, caused by the escape into them of the salt, will produce thirst and increased intake of fluid until their concentration is reduced to normal. The absence of the diuretic effect implies that there is no driving force pumping the excess of sodium chloride out of the blood, and therefore out of the tissues. These indeed seem to possess but little sensitiveness towards the presence of the salt, which forms the most abundant constituent of their normal medium.

It is a familiar circumstance that the ingestion of an excessive quantity of salt provokes thirst rather than diuresis. If this excessive ingestion were continued or became chronic, there would be a tendency for the amount of this salt in the body to continually increase, the salt being associated with sufficient water to maintain the molecular concentration of the body fluids at their normal height. It is not surprising therefore that excessive quantities of salt have been found to exert a deleterious influence in cases of dropsy, or that marked benefits as regards the reduction of dropsy have been attained by the limitation of salt in the diet.

Similar chemical factors might be involved in other cases, either where there is increase of the total fluid of the body without evident œdema, as in chlorosis, or in the universal œdema which occurs in Bright's disease. The responsible factor in these cases might be either—

(*a*) The production of some substance of low molecular weight which could be easily distributed through the tissues

and add to their molecular concentration, but which had no specific diuretic effect, or—

(*b*) A retention of the normal constituents of the body in consequence of deficient excretion by the kidneys.

The causation of the dropsy in Bright's disease is at present enshrouded in ignorance, and we cannot yet say how far it is really comparable to the waterlogged condition of the body which may be brought about by over-feeding with sodium chloride. It is important to remember that in every case, where we have disturbance of the balance between intra- and extra- vascular fluid, or of the balance between the intake and output of fluid into or from the body as a whole, we must take into account not only the mechanical conditions which determine transudation and absorption, but also the possible effects of chemical substances in their relation to excretion and absorption, as well as to the vitality of the capillary walls and tissue cells. Only by keeping these possible factors in view can we hope to arrive at some solution of the difficulties which present themselves when we attempt to account for the occurrence of dropsy in its manifold forms.

LECTURE VIII

THE CAUSATION OF DROPSY

From the practical point of view, the most interesting and important pathological alteration in the distribution of the fluids of the body is to be found in the condition known as dropsy. The term dropsy may be used to denote either an increased amount of fluid in the connective tissue spaces, especially of the skin, when it is sometimes designated as anasarca or œdema, or an accumulation of fluid in the serous spaces of the body, as in the conditions of hydrothorax and ascites. In some cases the production of œdema may be brought about by local changes, and therefore involve merely a different distribution of the body fluid. Often however, the increase of fluid in the connective tissue spaces, including the serous spaces, is more or less general, and may be associated with a simultaneous increase of the other chief fluid of the body, namely, the blood. Our previous studies enable us to enumerate a number of factors which might possibly be involved in the flooding of the tissue spaces which is characteristic of dropsy. I have drawn up a list of these factors in the form of a Table, and it will be my office in this lecture to attempt to assign to each of them its relative importance.

Factors involved in the Causation of Dropsy.

I. Factors causing increased transudation:—

A. Increased intra-capillary pressure:

a. Venous obstruction.

b. Vasodilatation.

c. Plethora.

I. Factors causing increased transudation—*continued.*

B. Increased permeability of vessel wall:

a. Local injury by mechanical irritants.

,, ,, ,, thermal ,,

,, ,, ,, chemical ,,

b. Malnutrition.

c. General injury by circulating poisons (?).

C. Watery condition of blood (hydræmia).

D. Increased molecular concentration of tissues.

II. Factors causing diminished absorption:—

A. By lymphatics:

a. Paralysis of limbs.

b. Obstruction of lymphatic trunks.

B. By veins:

a. Venous obstruction.

b. Watery condition of blood.

c. Concentrated transudations (*i.e.* in protein).

It is important to remember that probably under no circumstances can dropsy be ascribed to an abnormal change in one only of these processes. This however can also be said of any other diseased condition of the body. We know that the organism responds to a destruction of a considerable part of the excretory apparatus of the kidney by sending up the general blood pressure, and so driving an increased amount of blood through the still healthy glomeruli. But we cannot say that two-thirds of the kidneys are practically inactive under normal conditions, because excision of two-thirds causes no change in the general condition of the animal nor any appreciable heaping up of urea in the blood. In the same way we find that the organism has various powers of accommodating itself to changed conditions in its lymphatic apparatus, so that it is in most situations difficult to upset the normal balance—*i.e.*, cause dropsy—by altering only one of these factors, unless the alteration be of a very extreme degree. In nearly all cases the dropsy is

due to the simultaneous alteration of two or more of these factors. In the following lecture I shall try to show, so far as our imperfect experimental knowledge allows, which of these factors are affected in the chief forms of dropsy known clinically, and also to show how the normal balance between production and absorption has been in each case upset.

The form of dropsy which is simplest in its pathology is that which is due to venous obstruction. Clinically one meets with dropsy of one extremity due to obstruction of the veins draining that part, either in consequence of pressure by growths, or of thrombosis occurring in the vein itself. It would be natural to ascribe this dropsy to the increased lymph production consequent on the raised intra-capillary pressure behind the obstruction. On investigating the subject experimentally however, one finds that the causation is not quite so simple. Here, as in nearly all other cases, more than one factor is at work. It is a well-known fact that although obstruction of the femoral vein by a thrombus may give rise to pronounced œdema of the leg, yet ligature of the femoral vein or even of the lower end of the inferior vena cava in dogs produces no œdema of the legs. Thus Lazarus Barlow* found that elastic constriction of the veins of a limb, sufficient to cause a considerable rise of pressure in all the veins below the point of constriction but insufficient to interfere appreciably with the arterial supply, caused no diminution in the specific gravity of the tissues for, at any rate, one hour after the application of the ligature. We can however produce an œdema if we raise the intra-capillary pressure still higher than in these experiments. According to Paschutin † ligature of all the venous trunks of the dog's leg causes

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* *Phil. Trans.*, 1894, B., p. 779.

† Ludwig's *Arbeiten*, 1873, p. 95.

œdema of the foot and ankle. Ranvier* has shown that if, after ligature of the inferior vena cava, the sciatic nerve be divided on one side so as to produce dilatation of arterioles on that side, the limb in which the nerve has been divided will become œdematous. According to Cohnheim œdema may be brought about by injecting the veins of the leg with plaster of Paris. We see then that we can produce œdema in a limb provided we raise the intra-capillary pressure to a sufficiently high point. If only one or two veins be obstructed, the outflow by the collateral circulation is sufficient in a healthy animal to ward off any œdema. If the lymph be collected by placing a cannula in one of the lymphatics of the leg, it will be observed that after these severe obstructions it becomes red from the presence of red blood corpuscles. In the ordinary œdema of venous obstruction in man the lymph is generally perfectly clear, and the presence of red corpuscles shows that the rise of intra-capillary blood pressure under these circumstances is, so to speak, hyper-physiological, and is probably never attained under ordinary conditions either of health or disease. Why then do we not obtain œdema of the dog's leg by simple ligature of the vena cava or femoral vein? In man we know that obstruction of either of these two vessels frequently brings about œdema of the lower extremities, and that the œdema fluid present in the interstices of the tissues is colourless and free from red blood corpuscles, *i.e.*, corresponds to the lymph of moderate venous obstruction. The apparent discrepancy which is found here between clinical observations and the results of experiment depends on the fact which I have emphasised at the beginning of this lecture, namely, that it is impossible to upset the physiological balance, which prevents the occurrence of

* Comptes rendus, LXIX. 1869.

dropsy, by a moderate disturbance of either of the factors lymph production or lymph absorption. Such an enormous rise of capillary pressure, as is produced by filling all the veins of the leg with plaster of Paris, probably rarely or never occurs under clinical conditions. The occurrence of dropsy in man in consequence of venous obstruction is nearly always due to the simultaneous working of two or more factors. We have therefore to decide in the first place why, in a healthy animal with a moderate venous obstruction, no œdema is produced, and secondly what are the subsidiary factors which in man combine with the venous obstruction to bring about an œdema.

In considering the first point, it is essential to remember that in the case of œdema of the limbs we are dealing with the most impermeable capillaries in the body, so that under normal conditions a considerable capillary pressure is required to separate the lymph from the blood, and the lymph so separated has lost the greater part of its protein. I have already shown how, in consequence of this difference of composition between plasma and lymph, there is an accurate balance between the force tending to produce exudation—*i.e.*, the capillary pressure—and the force tending to produce absorption—*i.e.*, the difference of osmotic pressures between blood-plasma and lymph. If in a normal animal a vein be obstructed, the first effect is a rise of capillary pressure and increased exudation. Since however in the affected capillaries and veins the onward flow of blood is checked, the increased exudation must be at the expense of an increased concentration of the blood-plasma. This increase in concentration must cause an increase in the difference between the osmotic pressures of plasma and lymph, and the absorbing force :—*i.e.*, the osmotic pressure of the plasma, will rise until it is equal to the driving-out force—*i.e.*, the capillary pressure.

In a healthy dog with normal vessels the processes tending to cause œdema will be pulled up almost as soon as they have started, and no œdema will result from moderate venous congestion. It is easy now to see how we might cause œdema by venous congestion. In the normal animal the factor which restrains the appearance of œdema is the impermeability of the vessel wall, since it is this impermeability which maintains the difference in osmotic pressure between blood and lymph. If we can increase the permeability in any way, the balance of processes will be upset, exudation will predominate over absorption, and œdema will result. One method by which this may be effected is that of scalding. If the limb of an anæsthetised animal be plunged into water at 50° or 60° and kept there for some minutes, it is found that not only is the lymph flow from the limb increased, but that it now reacts immediately to changes in the capillary blood pressure, any rise of the latter, whether occasioned by arterial dilatation or by venous obstruction, causing immediately a great increase in the lymph flow from the limb. Moreover the lymph obtained under these circumstances is found to be more concentrated than that normally flowing from the limb, showing that the permeability of the capillary wall has been increased. It must be remembered that the capillary wall is alive and is composed of cells which have a metabolism of their own, and which, like all other cells of the body, are dependent for their proper nutrition on a free supply of oxygen and nutrient material and a free exit for their waste products. Their only function, so far as we know, is the maintenance of their integrity as a membrane with certain properties differing according to the region of the body in which they happen to be situated. If they are injured in any way, the resistance of the membrane is diminished and its permeability is increased. Such an injury will follow if they

be deprived for some time of a fresh supply of nutrient material and oxygen. Cohnheim showed that, after long-continued anæmia of the rabbit's ear, the vessels became so permeable that the restoration of the normal circulation was followed by pronounced œdema of all the tissues. If the anæmia be of shorter duration, no œdema is caused by restoration of the normal circulation, but can be called forth at once by ligaturing the principal vein draining the part. In the same way Lazarus Barlow found that if a limb had been deprived of blood altogether for an hour, on then admitting the circulation there was a marked increase in the amount of tissue fluid, and this increase was still more pronounced if the veins of the limb were constricted. Now a long-continued venous obstruction must affect the vessel walls in the same way as anæmia, since here also the cells will be starved or asphyxiated. Hence it is that, in the chronic conditions which give rise to venous obstruction in man, we have the production of œdema. Moreover, in man when dropsy occurs as the result of venous obstruction, there are generally other conditions present which tend to damage the vessel wall and so increase its permeability. Thus the mere presence of thrombosis points to a probable defective nutrition of the vascular endothelium, and is found most frequently in patients suffering from anæmia or allied changes in the blood. The occurrence of malignant growths in the neighbourhood of a vein is usually associated with a condition of cachexia, and therefore with an impoverished blood supply to the endothelium. We have experimental evidence that the circulation of watery blood through the vessels, if continued for some length of time, alters the vessel wall to such an extent that a moderate venous obstruction will produce œdema. Cohnheim has shown that, although ligature of the femoral vein causes no œdema in a healthy dog, it will do so if the animal be first rendered

hydræmic by bleeding repeatedly at intervals of a few days. It must be remembered that in this case we have still a third factor which helps in the production of œdema. A more watery plasma will filter more easily through the vessel wall, and the diminution of proteins in the plasma must be accompanied by a diminution of the osmotic pressure in the plasma, which is active in absorption. To sum up, we may say that œdema can never be brought about in the limbs by a moderate rise of venous pressure, provided that the capillaries retain their normal impermeability. Œdema will occur as soon as the permeability of the vessels is increased. The injury leading to this increase in permeability may be brought about in any of the following ways: (1) long-continued venous congestion (asphyxia of cells); (2) an excessive rise of intra-capillary pressure breaking down the normal resistance of the cells; and (3) malnutrition due to an impoverished state of the blood.

The relative importance of these three factors is well brought out in some recent experiments by Bolton.* This observer devised a very ingenious method for causing any degree of obstruction of the big venous trunks, *i.e.*, the superior vena cava, or inferior vena cava, or the portal vein. We shall have occasion directly to turn to the bearings of his experiments on the causation of the dropsy which occurs in heart disease, but we may consider here shortly the results obtained by him on constriction of the superior cava. The constriction was effected by encircling the vein with a split segment of a gum elastic catheter, which was bound round the vein. By this means it was possible to occlude the vein completely or to diminish its lumen to any desired extent. He found

* Charles Bolton, "On the Pathology of the Dropsy produced by Obstruction of the Superior and Inferior Venæ Cavæ and the Portal Vein," Proc. Roy. Soc. B., Vol. LXXIX., 1907, p. 267.

that in every case where the lumen was diminished to three-fifths of the normal amount, *i.e.*, sufficient to cause an appreciable rise of pressure in the jugular vein, œdema was produced within one or two days. The œdema affected the superior mediastinum, the tissues of the neck, and in most cases, owing to the drainage of the fluid from the mediastinal tissues into the pleural cavities, there was hydrothorax on both sides. The effects were more marked when the obstruction was placed below the azygos vein, *i.e.*, between this vein and the heart. Since the obstruction was always followed by a rise of venous pressure in the jugular vein and by a distension of all the veins of the neck, it might be thought that the experiment afforded a striking confirmation of the important part played by rise of pressure in the production of dropsy; but Bolton found that, if the venous pressure in the jugular vein were measured a few hours after the obstruction had been produced, although the veins were still distended, the pressure in them had fallen to a point that was approximately normal. The only mechanical change present therefore was a stagnation of the blood in dilated veins. Although at the point of obstruction itself, owing to the stagnation and the consequent absence of fall of pressure from periphery to centre, the pressure would be somewhat above normal, Bolton is justified in concluding that there can be no appreciable rise of pressure in the capillaries which are responsible for the increased transudation. Yet this increased transudation and the production of dropsy is proceeding rapidly at a time when the pressures have fallen, and one is therefore driven to the conclusion that the essential factor here is not rise of pressure, but the alteration of the vessel wall consequent on stagnation of blood and privation of oxygen. The alteration in the muscular tissue of the veins is shown by the fact that they are distended to a large extent

under a normal pressure. The alteration in the endothelium of the capillary wall must be regarded as the essential factor in the production of the œdema. It is possible that the malnutrition of the extra-vascular tissues may also play some part in the production of œdema, *e.g.*, by the production of injurious disintegrative products or by disorganisation of the elastic framework of the tissue spaces.

Much more frequent than the œdema due to local venous obstruction is the œdema which occurs as a consequence of uncompensated or imperfectly compensated heart disease. In this class of cases we have much more complicated conditions than in the class I have just discussed. The œdema of heart disease is generally looked upon as obviously due to a rise in venous pressure and consequent venous obstruction. Taking the existence of a high pressure on the venous side of the heart in such cases as a fact, we have to inquire into the causes for this rise of pressure and whether this rise of pressure will extend to the capillaries. To investigate the causation of the dropsy in heart disease therefore, we must take into account the alterations in the circulation as well as the alterations in the absorption and production of lymph. The vascular system in an animal can be looked upon as a closed system of tubes having a definite capacity. If the circulation were brought to a standstill, the pressure at all parts of the system would become the same. This pressure is called the mean systemic pressure, and in a dog is equal to about 10 mm. Hg. Now in such a system it is evident that the height of this mean pressure depends solely on the relation between the amount of contained fluid and the capacity of the system. If circulation be established by means of the heart's beat, the relation between the capacity and the volume of blood remaining unchanged, no alteration can occur in the mean pressure. All we have is an alteration

in the distribution of the pressure. Behind the heart—that is to say, on its venous side—the pressure will sink below the mean systemic pressure; on the arterial side the pressure will be raised above the mean pressure. If after the establishment of the circulation the action of the heart-pump be interfered with, as by damage to the valves, or be checked altogether, the pressures on each side will tend to return to the zero of the system—*i.e.*, the mean systemic pressure. As a result there will be a fall of arterial pressure and a rise of venous pressure to this point. It becomes important to know at what point in the system the pressure, while the circulation is going on, is equal to the mean systemic pressure.

In a series of experiments which I carried out many years ago with W. M. Bayliss * we came to the conclusion that this turning point of the circulation, so to speak, is situated in the region of the hepatic capillaries in the abdomen and at about the level of Poupart's ligament in the femoral vein. Failure of the heart-pump would cause a rise of pressure in the vena cava and in the large veins of the neck, but a fall of pressure in the portal vein, in the peripheral veins of the legs, as well as in the arteries. It would seem therefore that failure of the heart's action, to whatever cause it may be due, can only bring about a fall of pressure in the capillaries of the intestines and peripheral parts of the body. Any general constriction of the arterioles would, however, raise the mean systemic pressure, so that failure of the heart, if it were followed by constriction of the arterioles, would cause a rise of pressure above normal which might extend as far as the peripheral end of the veins of the leg. Bolton, as a matter of fact, has found a distinct rise of pressure in the veins of the foot as a result of interference with the action of the heart so

* Bayliss and Starling, *Journ. of Physiol.*, XVI., 159, 1894.

as to imitate the condition which is present in failure of compensation. There can be no doubt that this rise of venous pressure would be aided by the condition of plethora which, as I have shown in my last lecture, is probably an almost invariable concomitant of chronic failure of compensation. It seems very doubtful, however, if not absolutely disproved, that, even in marked cases of failure of compensation, one is justified in predicating a rise of pressure in the capillaries of the body above its normal extent. Indeed, it results from Bolton's experiments on this subject that œdema may occur under conditions in which the capillary pressure is certainly not higher than in the normal animal. Bolton imitated the conditions in failure of compensation in two ways. In the first series of experiments he interfered with the diastolic dilatation of the heart by constricting the pericardium by means of ligatures.* In a large number of cases he obtained survival of the animal and the production of ascites, *i.e.*, accumulation of fluid in the abdominal cavity. In another series of experiments Bolton caused a simultaneous constriction of the superior cava and of the inferior cava, the former being constricted by means of a catheter to three-fifths of its normal dimensions, and the latter also to two-thirds.

The results obtained are of such importance for the understanding of the conditions in heart disease, that some of the experiments may be here quoted.

In the following experiment the effects of constriction of the pericardium on the arterial and venous pressures were observed:—

Cat. Weight 3,000 grams. Anæsthetised with ether; tracheotomy and artificial respiration. Cannula in right femoral artery; cannula also

* C. Bolton, "The Experimental Production of Uncompensated Heart Disease, with especial Reference to the Pathology of Dropsy," *Journ. of Pathology*, IX., 67, 1903.

introduced into a branch of the left femoral vein, just above the foot, and pushed down till it just reached the opening of the branch into the main trunk.

Pressures at beginning of the operation:—

Artery.		Vein.
110 mm. Hg.	.. ..	140 mm. $MgSO_4$ solution.

1. *Pericardium constricted with Forceps.*

The pressures at once altered as follows, the presystolic pulsation in the vein, together with the rises in pressure synchronous with insufflation of the lungs being very evident:—

		Artery.		Vein.	
..	..	50 mm. Hg.		175 mm. $MgSO_4$ solution.	
In 5 minutes	..	50	,,	160	,, ,,
,, 5 ,,	..	40	,,	155	,, ,,
,, 10 ,,	..	48	,,	150	,, ,,
,, 5 ,,	..	60	,,	148	,, ,,
,, 5 ,,	..	70	,,	150	,, ,,
,, 5 ,,	..	78	,,	146	,, ,,
35 ,,					

2. *Pericardium further constricted.*

		Artery.		Vein.	
..	..	60 mm. Hg.		164 mm. $MgSO_4$ solution.	
In 5 minutes	..	60	,,	155	,, ,,
,, 5 ,,	..	70	,,	148	,, ,,
,, 5 ,,	..	70	,,	143	,, ,,
15 ,,					

3. *Pericardium constricted still further.*

		Artery.		Vein.	
..	..	50 mm. Hg.		150 mm. $MgSO_4$ solution.	
In 5 minutes	..	48	,,	145	,, ,,
,, 10 ,,	..	50	,,	140	,, ,,
15 ,,					

The pericardium was now released, and at once the pressures became—

		Artery.		Vein.	
..	..	80 mm. Hg.		100 mm. $MgSO_4$ solution.	
In 3 minutes	..	80—90	,,	95	,, ,, No venous pulse.
,, 5 ,,	..	90—100	,,	85	,, ,,
8 ,,					

4. *Pericardium again constricted.*

	Artery.	Vein.
..	.. 40 mm. Hg.	120 mm. $MgSO_4$ solution.
In 5 minutes	.. 50 ,,	150 ,, ,,
,, 30 ,,	.. 50 ,,	130 ,, ,,
,, 15 ,,	.. 46 ,,	123 ,, ,,
,, 5 ,,	.. 50 ,,	130 ,, ,,
,, 5 ,,	.. 52 ,,	130 ,, ,,
1 hour		

The pericardium was now released, and at once the pressures became—

Artery.	Vein.
80 mm. Hg.	80 mm. $MgSO_4$ solution.

This experiment shows that, although there is a rise of pressure in the femoral vein synchronous with the fall of arterial pressure, the venous pressure subsequently falls to its normal level in the course of an hour or so. This fall of venous pressure is not due to gradual stretching of the pericardium, since the arterial pressure remains at the low level to which it was reduced by the constriction.

Similar results were obtained by obstructing the superior together with the inferior vena cava. Thus on completely ligaturing the superior cava and constricting the inferior cava to a diameter of 3 mm. the arterial pressure fell considerably, while the venous pressure rose. In a few hours the venous pressures, taken in the peripheral ends of the jugular and femoral veins, often fell to normal. In every case however dropsy was produced, fluid being found a few days later in each pleural cavity, in the peritoneal cavity, and in the mediastinum. It is especially important to note that the dropsy was produced at a time when the venous pressures had fallen to normal.

The effects of constriction of the inferior cava on the blood

pressure in different parts of the body may, according to Bolton, be summed up as follows:—

Immediate Result:—
Rise of pressure in capillaries of trunk.
,, ,, ,, ,, ,, feet.
Fall of pressure in capillaries of head.
,, ,, ,, all arteries of body.

Result in 1—1½ *hours:—*
Trunk and feet normal.
Head below normal.
Arterial pressure below normal.

Later:—
Trunk normal or raised.
Feet below normal or normal.
Head below normal.
Arterial pressure below or normal.

This observer regards the later rise of venous pressure in congested area and in arteries as dependent entirely on vaso-constriction, and not on absorption of fluid, though he himself shows that there is an absorption of fluid in the areas of low pressure to replace that lost as dropsy in the congested areas. I am still inclined to think that both factors play an important part in the production of the complex of symptoms observed in failure of compensation. Bolton's results show clearly that a condition of plethora or of raised capillary pressure are neither of them necessary for the production of œdema. It may be noted that in all the experiments the veins were dilated so long as the increased transudation was occurring. The pressures, however, in the peripheral parts of the veins, *i.e.*, in the jugular vein and in the femoral vein, varied within normal limits. The venous wall was therefore altered so as to dilate abnormally under pressures which were normal. Since the arterial pressure was either subnormal or normal, we have no grounds for assuming that there was any rise of capillary pressure to account for the production of the

œdema; the essential factor here, as in the case of obstruction of a vein, is stagnation of the blood. There is from these capillaries an increased transudation under normal pressure: that is to say, the permeability of the capillary endothelium is altered as a result of defective nutrition.

In heart disease a fact is present which is not operative in simple venous obstruction, namely a hindrance to the outflow by the lymphatics in consequence of the rise of pressure and stagnation of the blood in the superior vena cava near the heart. The same rise of pressure, which we must assume to be confined to the big veins in the immediate neighbourhood of the heart, will probably cause a rise of capillary pressure in the liver, and this is seen in the swelling and pulsation of this organ which is a constant result of failure of the normal pumping action of the right heart. The flow of lymph from this organ must therefore be largely increased, and probably this liver lymph contributes appreciably to the production of ascites, which is one of the earliest phenomena following failure of the heart's action. The production of dropsy in heart disease is thus by no means simple. It involves a complicated series of interacting mechanisms, all of which tend to the death of the organism. We may sum up the sequence of events which ensue on failure of compensation as follows:—

Stage I.—Heart-pump failure; fall of arterial pressure and rise of pressure in the venous trunks; fall of capillary pressure in the peripheral parts of the body, in the kidneys, and in the intestine.

Stage II.—The organism attempts to keep up the arterial pressure, which determines the blood supply to the brain, by constriction of the arterioles. Arterial pressure is thus raised to a certain degree; the venous pressure is raised still higher than before, so that the rise extends to the venous radicles in

the tissues. It is doubtful whether there is any actual rise of capillary pressure.

Stage III.—By the dilatation of the veins the venous pressure tends to sink. The inadequate filling of the arterial system calls forth an increased intake of fluid into the blood. We therefore get a series of conditions tending to increase the blood fluid at the expense of the tissue fluid and a continual effort by a rise of venous pressure to stimulate the failing heart so that it can pump sufficient blood into the contracted arterioles.

Stage IV.—Before however any large alteration in the total volume of blood has time to take place, the capillary walls begin to suffer from the stagnation of the blood consequent on the failure of the heart-pump. Wherever, therefore, the normal pressure in the capillaries due to the heart is raised by hydrostatic pressure due to gravity, there is an increased transudation and an accumulation of fluid in the connective tissues. In the animal at rest the first sign of increased transudation occurs in the abdominal organs, especially in the liver. Next we get the increased transudation in the mediastinal tissues. In man, with the assumption of the erect position, the pressure of the blood on these capillaries is relieved at the expense of those of the lower part of the body and legs, so that there is diminution of the hydrothorax and ascites, but production of œdema in the lower extremities.

In both these classes of dropsy therefore, the primary factor is an alteration in the mechanical conditions of the circulation. As a result there is altered nutrition of the capillary wall, increased permeability, and production of dropsy.

In the next class with which we have to deal, the primary change affects, not the mechanical conditions of the circulation, but the vessel wall. A change of the filtering membrane is thus

produced, so that it becomes more permeable, and allows, under normal capillary pressures, an excessive exudation, and the exudation is richer in protein than is the normal lymph of the region in question. Since an alteration of the vessel wall is one of the main features of inflammation, Cohnheim has classed all œdemas, in which the primary affection is that of the vessel wall, as inflammatory œdemas. I have already pointed out various means by which the permeability of the capillary wall might be increased, and showed how, under these circumstances, the limb capillaries might be reduced to the condition of liver capillaries. Here, as in all other cases in which œdema occurs, we have more than one factor at work. The capillary pressure of the part remaining at its normal height, the increased permeability allows of a largely increased exudation—there is increased lymph production. The lymph however contains more proteins than normal, so that the difference of osmotic pressure between it and the circulating plasma is diminished, thereby causing a diminution of the absorbing force. In all cases of inflammatory œdema these two factors are at work concurrently: increased production and diminished absorption. This alteration of the vessel wall may be brought about in two ways, either by the application of injurious agents to the vessels of any given part, or by the introduction of poisonous substances into the blood stream. Thus a local alteration of the vessel wall may be caused by application of mechanical violence, crushing the tissues. It is possible that in this case we have at work, not only the direct result of the injury on the vessel wall, but also a secondary injury of the capillaries in consequence of the development of poisonous products of disintegration in the bruised tissues surrounding the capillaries. We can produce the same change by exposing the tissues for a few minutes to a temperature of over 50° C., or by depriving them

for some time of the normal blood-flow. All the local œdemas produced by inoculation of chemical or microbic poisons at the point of inoculation are of this nature. The swelling produced by the sting of a bee, or by the inoculation of anthrax, is due to the deleterious effects of the poison on the capillary walls at the point of inoculation. Metchnikoff showed that the emigration of white blood corpuscles occurring in inflammation is to be looked upon as a physiological reaction of the organism directed to its preservation, and it seems probable that the salutary import of this process may also hold good for the local œdema. As the result of the injury of the capillary walls, a more concentrated lymph is poured out, *i.e.*, a lymph containing more proteins to serve for the nutrition of the cells of the part. Whether or not this is the case, the presence of this concentrated lymph must be of great use to the organism in the regeneration of tissue which follows on inflammation.

We know less clinically of the cases in which the injury to the vessel wall is brought about by a poison circulating in the blood. I have already described to you the class of animal poisons which were grouped together by Heidenhain as his first class of lymphagogues. The chief action of these bodies is on the capillaries of the liver. Their action, however, is not absolutely confined to this organ. I have experimental evidence that there is a certain degree of increased permeability of the intestinal capillaries after the injection of these bodies—an increased permeability which is brought into evidence only after raising to a certain extent the pressure in these capillaries. These bodies, however, can also affect the capillaries of the skin. In a number of the experiments in which these bodies have been injected, we may observe a rapid development of an urticarial eruption on the skin, and you are all familiar with the fact that the

ingestion of the animals from which these bodies are derived (mussels, crayfish, lobster) is often followed in man by an eruption of urticaria, which may or may not be accompanied by other symptoms of poisoning. The sudden onset of urticaria and similar eruptions in man, combined with the fact that their distribution may correspond with that of a certain nerve, has given rise to the supposition that these œdemas may be nervous in origin: that, in fact, we have an increased production of lymph under the direct influence of the nervous system. If lymph were to be looked upon as a secretion, we should expect, from analogy with other secretions, to find it subject to the central nervous system, and at one time I made diligent search for direct evidence of the influence of the nervous system on lymph formation. The results of my experiments were however opposed to such an hypothesis. In every case where nerve section or nerve excitation gave rise to increased lymph production in any part, I found that the increase was due primarily to a rise of capillary pressure in the part, and was therefore only a secondary effect of the interference with the nerve. The best-marked case of so-called nervous œdema is the unilateral œdema of the tongue, which may be produced by stimulating one lingual nerve. The stimulation of the lingual nerve causes extreme vaso-dilatation of the vessels of the tongue, and the increased lymph production in the tongue is evidently the direct result of this vaso-dilatation and consequently increased capillary pressure. Here, as in all other cases where one wishes to produce œdema, one must not rely simply upon one factor. In the majority of cases the œdema produced by stimulating the lingual nerve, *i.e.*, by a simple rise of capillary pressure, is but slightly marked. One can however produce a very fine œdema of the tongue if one aids the filtration process and diminishes

the forces tending to absorption by the injection of a large amount of normal saline solution into the circulation. I believe that all cases of so-called nervous œdema can be explained by the circulation of some lymphagogue substance in the blood combined with local vaso-dilatation, which may often be hysterical or central in origin. More evidence is, however, required on this point before we can claim to thoroughly understand the causation of the so-called angio-neurotic œdemas.

One of the most important forms of dropsy, *i.e.*, that which accompanies renal disease, was placed by Cohnheim in the category of inflammatory dropsies. One objection to this view is afforded by the fact that in the dropsy of Bright's disease we obtain an œdema fluid which is less concentrated than that found under any other circumstances, whereas in the changes in the capillary endothelium brought about by inflammation there is always an increased permeability of this endothelium, and therefore an increased amount of protein in the tissue fluid and lymph. Although in Bright's disease the blood-plasma may also be more dilute than normal, the diminution in its concentration does not seem sufficient to account for the very low protein content to be observed in the œdema fluid of the same disease. The discovery of lymphagogues naturally suggested that the change in the vascular endothelium in Bright's disease, which was assumed to be responsible for this increased permeability, was due to the circulation in the blood of some poisonous substance belonging to this group of bodies, and lymphagogue effects have been obtained in the dog on the intravenous injection of blood serum derived from an uræmic patient. Here too however, if we were dealing with increased permeability, we should expect to find a raised protein content in the œdemic fluid. At the present time it is impossible for us

to come to any conclusion as to the causation of the œdema of renal disease, though it seems probable that the causation is to be sought rather along the lines indicated in my last lecture, *i.e.*, by the accumulation of substances of low molecular weight in the tissues and the osmotic attraction of fluid by their means, than as a result of an increased permeability of the vessel wall similar to that found in inflammatory conditions.

This cursory examination of the alterations in physiological conditions present in the various forms of dropsy brings to light one important fact, a fact on which much stress has already been laid by Cohnheim. In all cases the primary cause of œdema is an increased transudation. The normal mechanism of absorption may for some time hold this process in check, but whenever the increased exudation endures any length of time, subsidiary events cause a breakdown of the absorbing mechanism and the occurrence of œdema. On the other hand, we know of very few cases in which œdema can be ascribed primarily to a diminished absorption. Obstruction of the lymphatics can rarely occur, owing to the multitudinous anastomoses of these canals. When a complete obstruction does take place, the result seems to be rather a general hypertrophy of the connective tissues, as in elephantiasis, than a true œdema. In all cases however where we find dropsy, we may say that, in addition to the primary increased exudation, there is a derangement of some part of the absorbing mechanism.

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